The American Journal of Medicine

August 1955

The American Journal of Medicine

The American Journal of Medicine is published monthly by The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, N. Y. Yearly Subscription, $12.00 *U. S. A.;* $13.00 *Canada;* $15.00 *Foreign, including Latin-American countries, Single Numbers* $2.00*; Symposia Numbers* $4.00. *Entered as Second Class Matter June* 28, 1946, *at the Post Office, New York, N. Y., and on June* 28, 1946, *at York, Pa., under the act of March* 3, 1879. *August,* 1955—*Volume* XIX, *No.* 2.

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

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The American Journal of Medicine

Vol. XIX AUGUST, 1955 No. 2

Editorial

Clinical Studies

This interesting study demonstrates that in some patients receiving digitalis, and at or near the point of digitalis intoxication, the administration of carbohydrate orally or intravenously may precipitate overt electrocardiographic indications of digitalis toxicity in the form of increased ventricular arrhythmias. This effect is ascribed to the well established lowering of the potassium concentration of arterial blood after carbohydrate ingestion, although no concomitant analyses were made by the author. The implications of practical concern are obvious. On this account, and because of intrinsic interest, further study of this phenomenon seems indicated.

In this interesting study the authors begin with a detailed description of the various forms of triple or three-sound rhythms and their physiologic and clinical significance. The chief concern of the authors is, however, with identification of the true gallop sound. They propose, as a simple bedside aid to differentiation, carotid sinus pressure (particularly on the right) which slows the usually rapid ventricular rate and causes the true gallop sound to become inaudible but makes other types of extra heart sounds more apparent. Illustrative cases with appropriate phonocardiograms and electrocardiograms are cited.

It is becoming apparent that next to the tetralogy of Fallot the most frequent form of cyanotic congenital heart disease, associated with polycythemia and clubbing, is pulmonary stenosis with interatrial communication. Clinically, the differentiation from the tetralogy of Fallot may be difficult and this presentation of clinical and hemodynamic data in ten cases is, therefore, of considerable value. Of special interest is the ingenious use made of selective injection of T-1824 dye to detect the presence, site and size of right-to-left shunts. Surgical implications are discussed.

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NOW

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eminently readable and enlightening, if sometimes arbitrary analysis and synthesis of the relevant experience. Dr. Engel first reviews the available anamnestic and psychoanalytic studies in their several significant components, then proceeds to correlative studies, gives a critique of psychologic formulations and ends with his own attempt at a psychosomatic formulation insofar as the available data permit such an attempt. Altogether, a notable contribution to this subject and one which should hold the attention also of the non-psychiatrically trained physician.

Seminars on Carbohydrate Metabolism

Dr. Stadie in this excellent orientating article summarizes the present status of knowledge of the complex actions of insulin on intermediary metabolism. He considers in some detail the permeability or transfer hypothesis of insulin action, the hexokinase theory, the effects of insulin on oxidative phosphorylation and the possible action of insulin on oxidative reactions in the Krebs cycle. The important role of insulin in the relationships between carbohydrate and fat metabolism is discussed. There is a brief statement of the major findings in connection with fixation of insulin by tissues.

Clinico-pathologic Conference

Clinico-pathologic Conference (Washington University School of Medicine).

Research Society Abstracts

Case Reports

The absence of gamma globulins from the blood, and of the antibodies included therein, has become a well recognized syndrome in children as the expression of a genetically transferred defect

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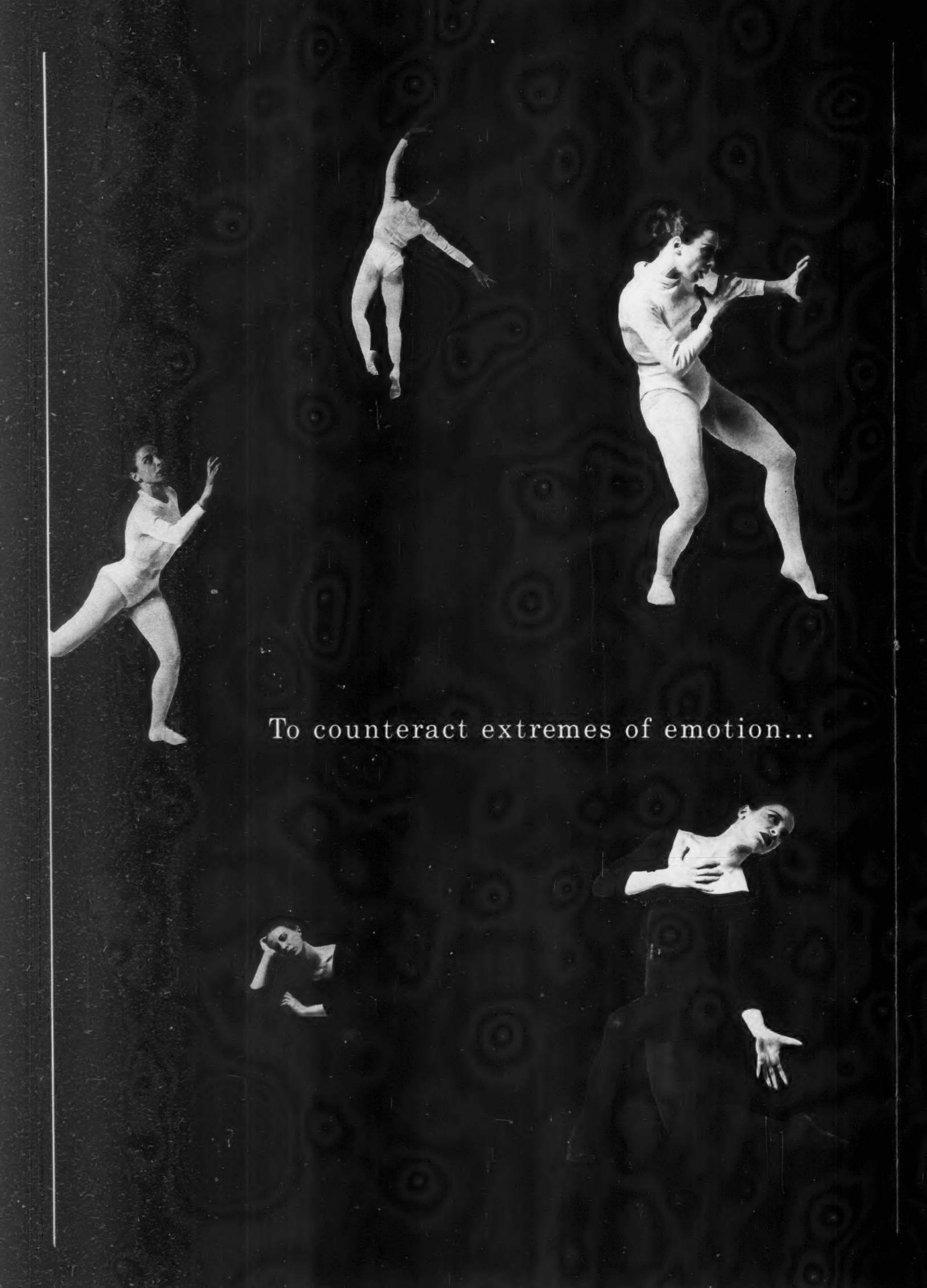
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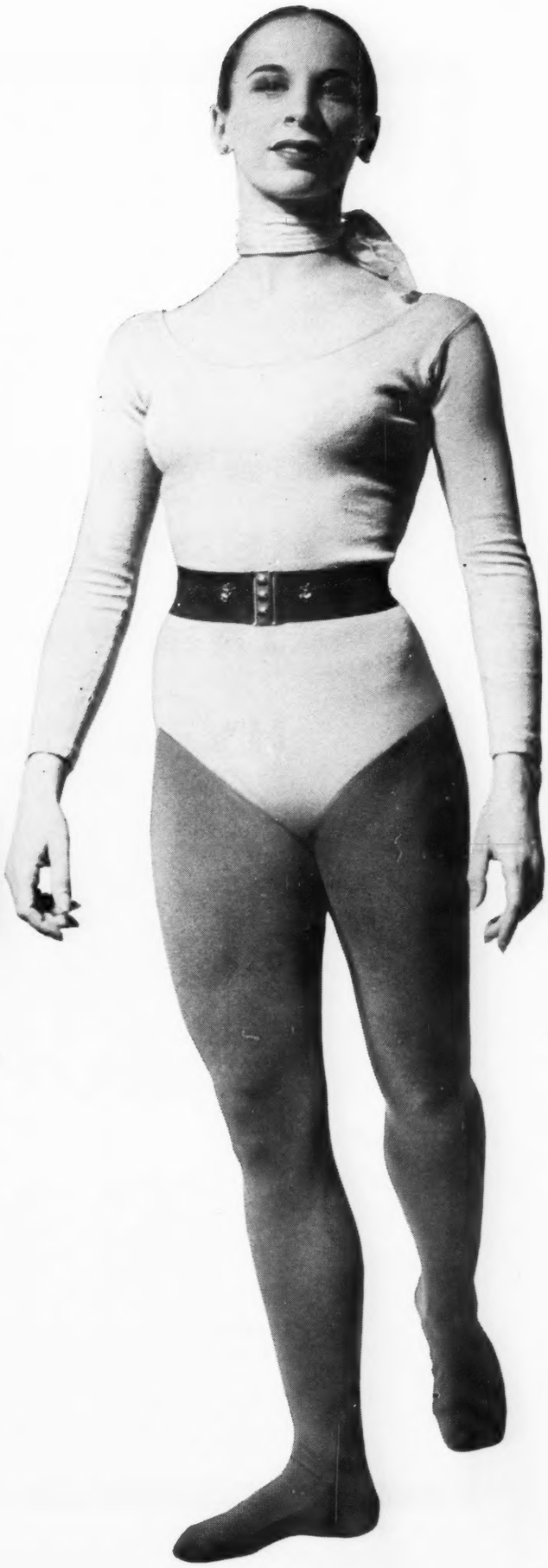

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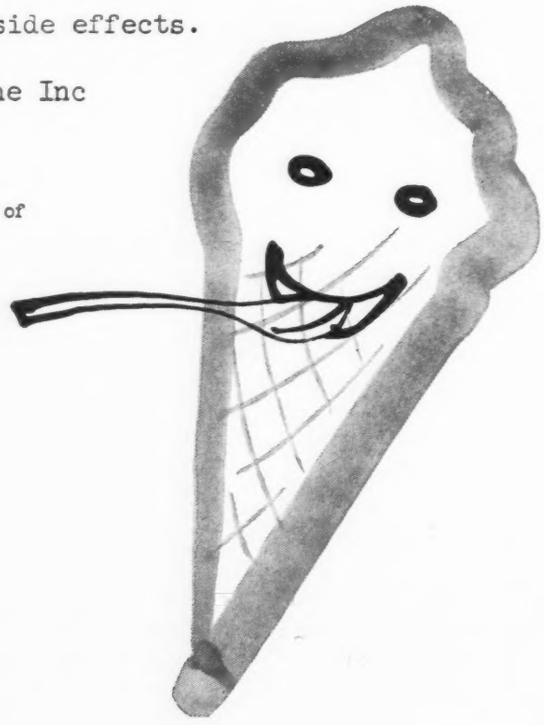

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1. Vernon, S.: Nutritional Deficiency, Clin. Med., Oct., 1950.

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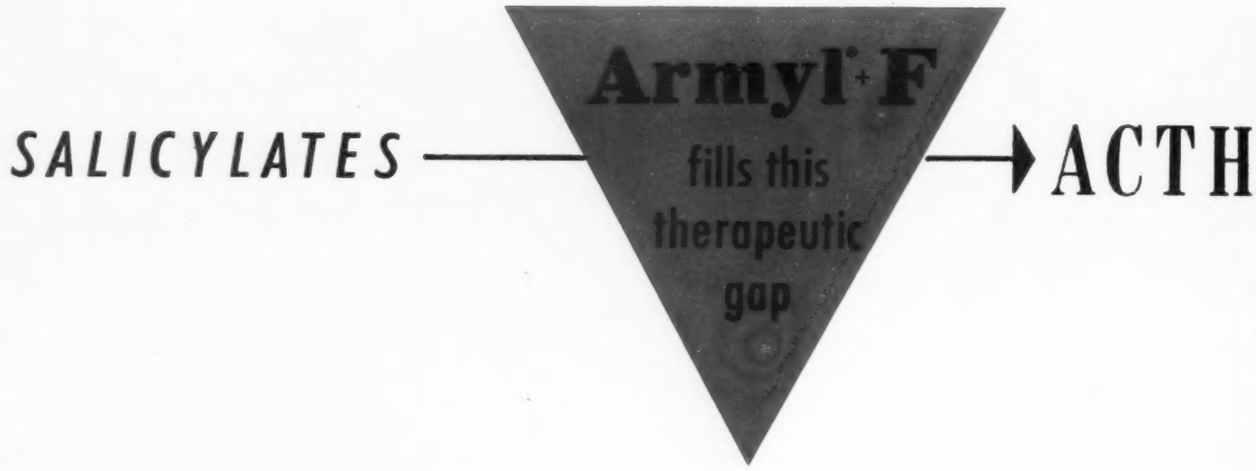
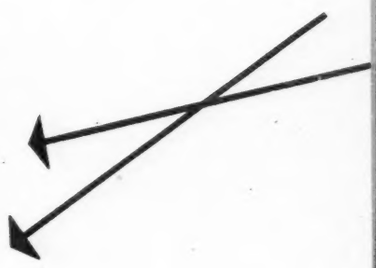
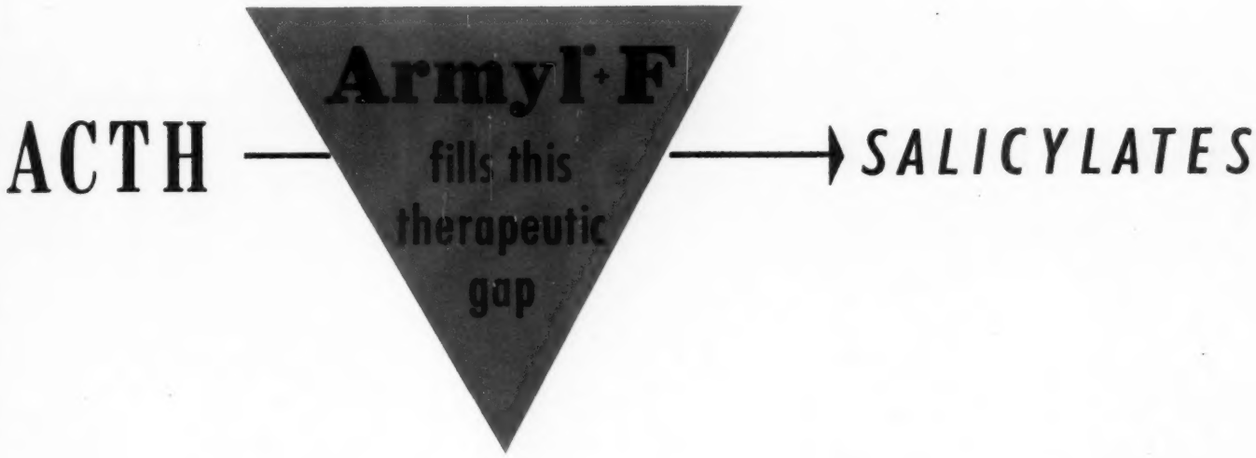


In the patient who fails

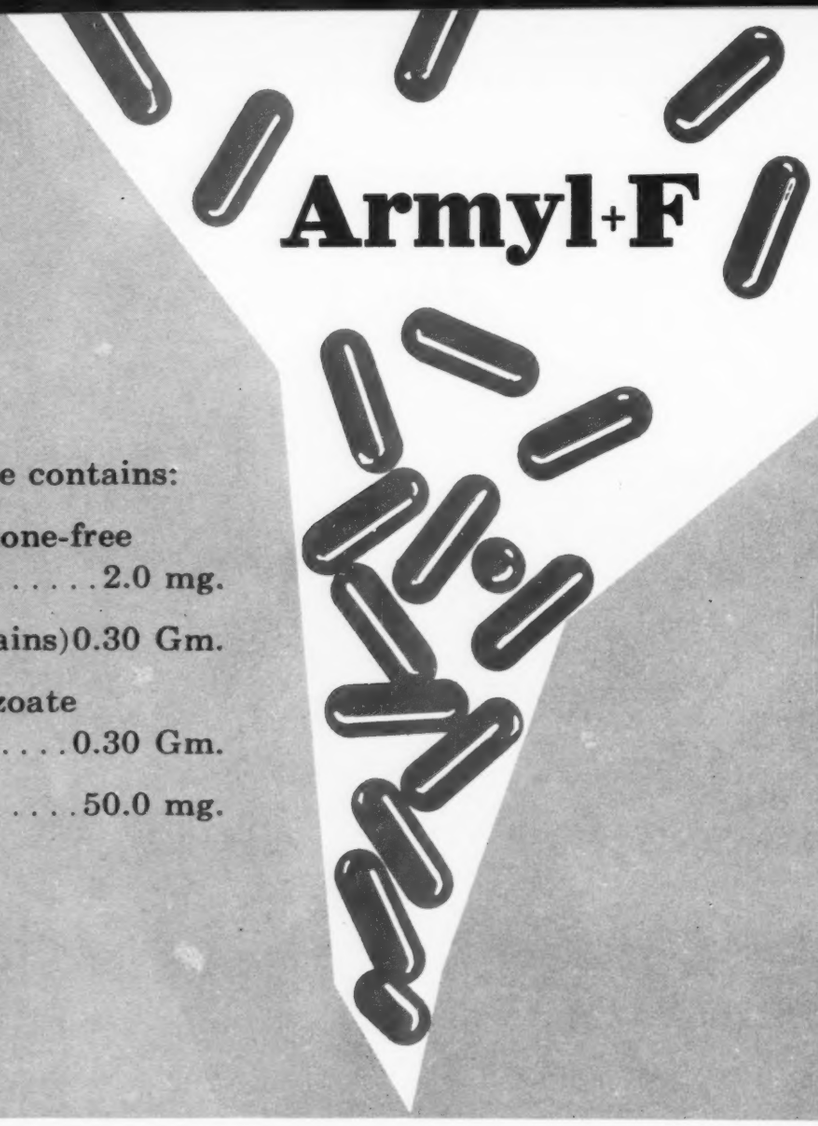
to respond to salicylates alone

THERE IS A GAP AFTER
THE STAGE OF **ACTH** THERAPY
IN ACUTE CONDITIONS





In the patient who
needs long-term management
of residual symptoms



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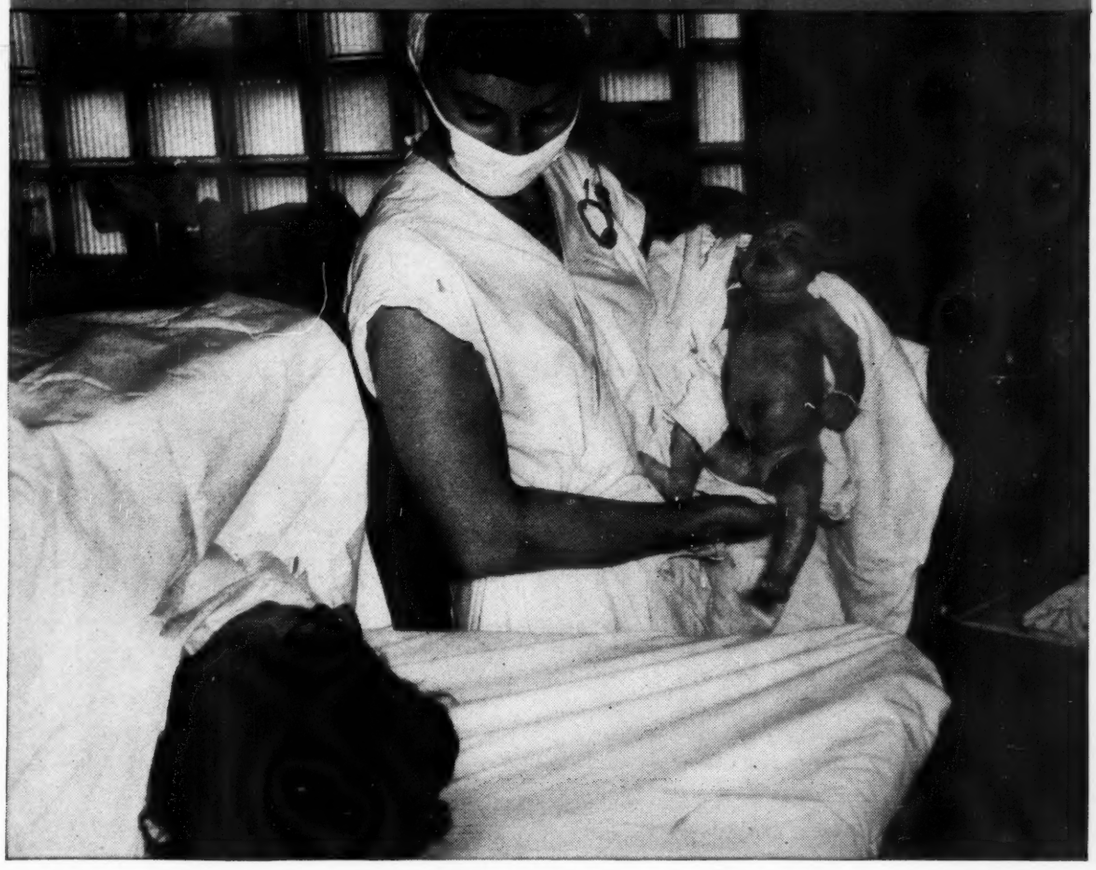

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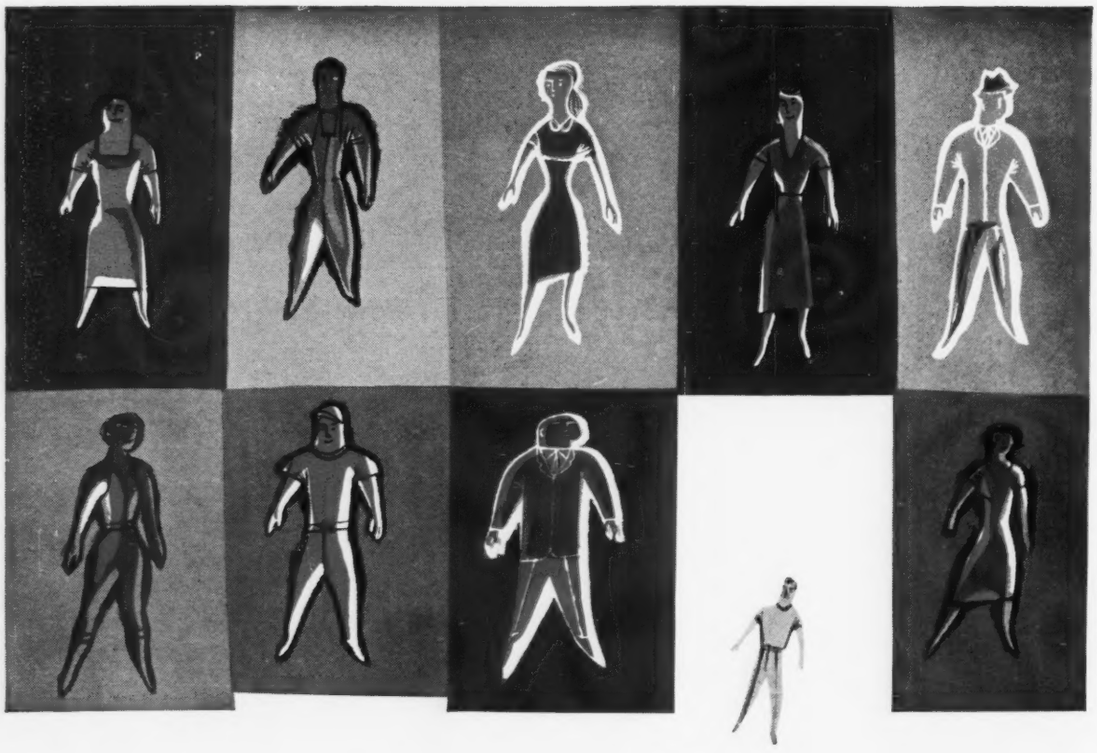

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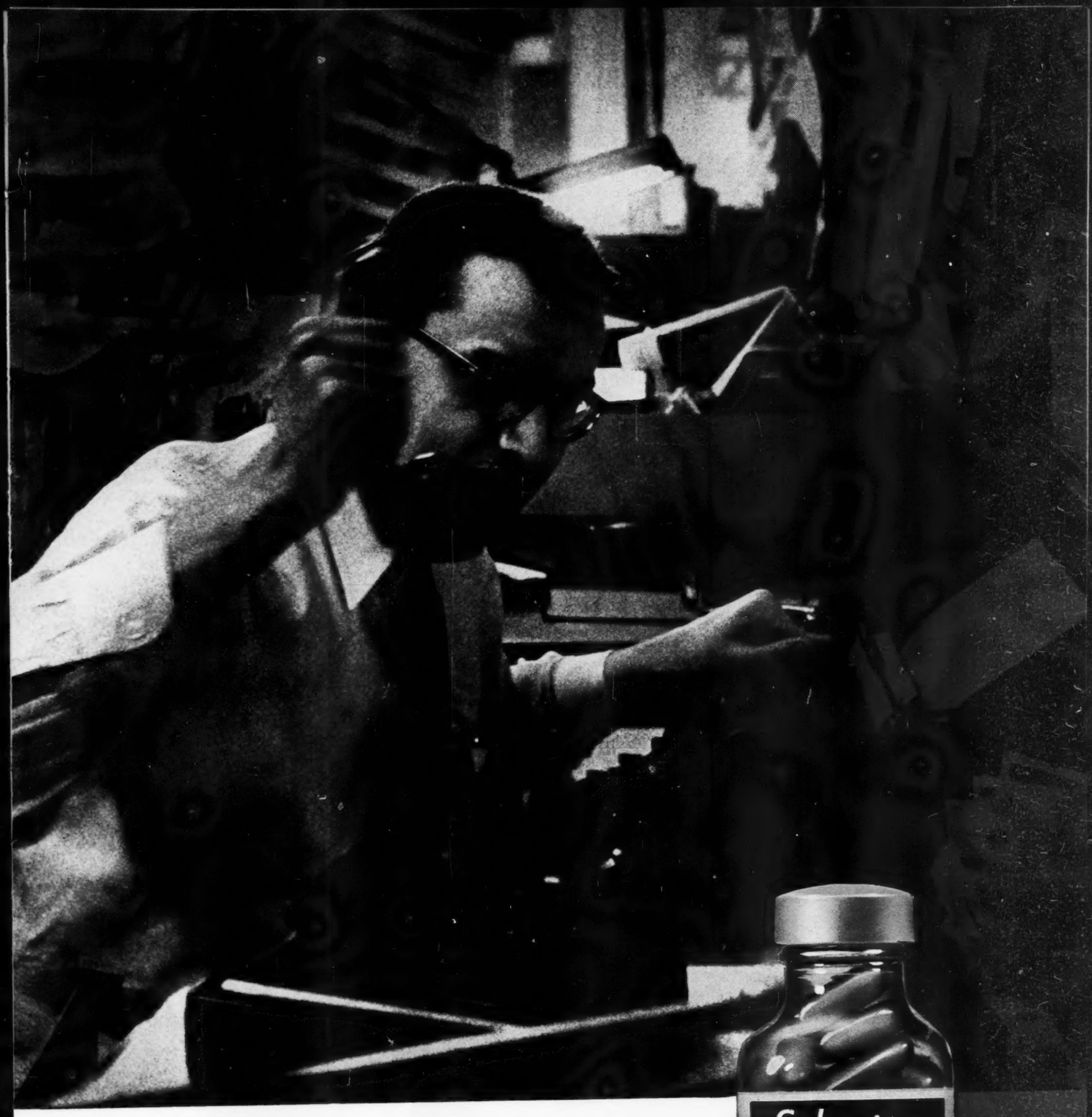

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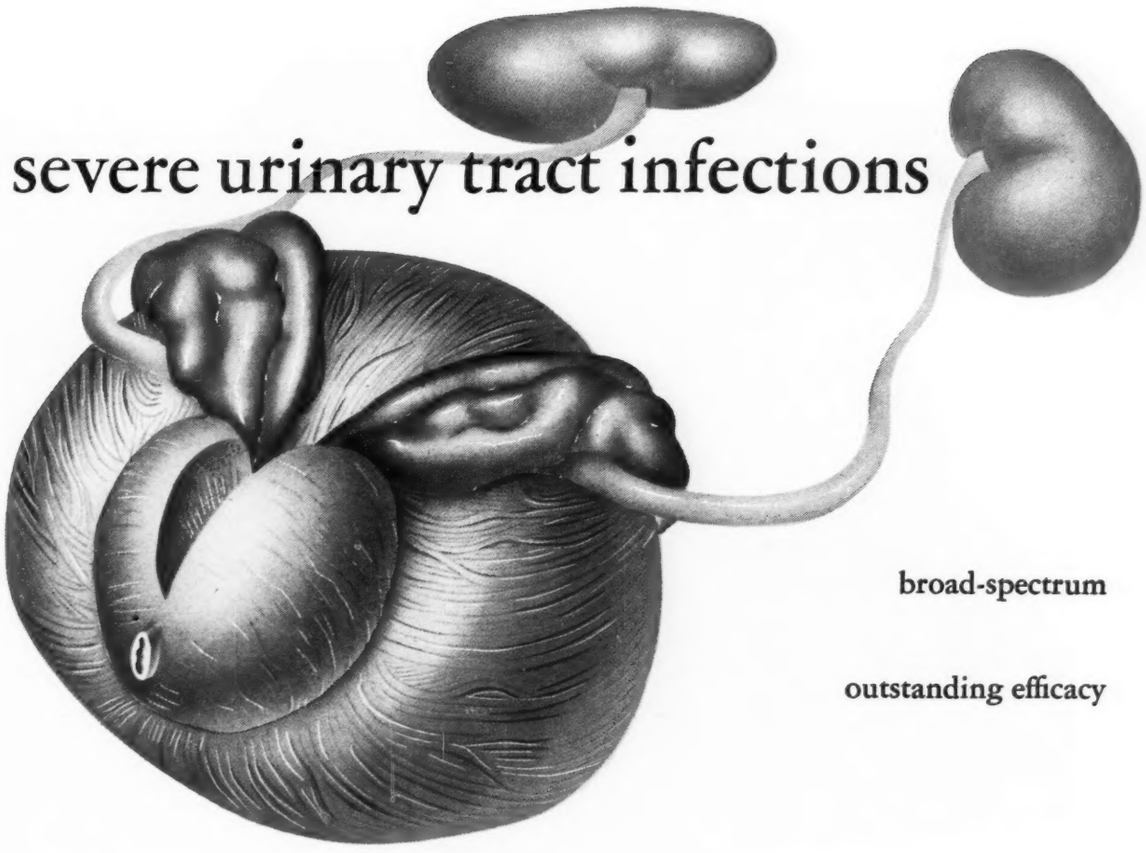

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References

(1) Jones, C. P.; Carter, B.; Thomas, W. L., & Creadick, R. N.: *Obst. & Gynec.* 5:365, 1955. (2) Balch, H. H.: Mil. Surgeon 115:419, 1954. (3) Altemeier, W. A.; Culbertson, W. R.; Sherman, R.; Cole, W., & Elstun, W.: *J.A.M.A.* 157:305, 1955. (4) Kutscher, A. H.; Sequin, L.; Lewis, S.; Piro, J. D.; Zegarelli, E. V.; Rankow, R., & Segall, R.: *Antibiotics & Chemotherapy* 4:1023, 1954. (5) Clapper, W. E.; Wood, D. C., & Burdette, R. I.: *Antibiotics & Chemotherapy* 4:978, 1954. (6) Sanford, J. P.; Favour, C. B.; Harrison, J. H., & Mao, F. H.: *New England J. Med.* 251:810, 1954. (7) Sanford, J. P.; Favour, C. B., & Mao, F. H.: *J. Lab. & Clin. Med.* 45:540, 1955. (8) Felshin, G.: *J. Am. M. Women's A.* 10:51, 1955.

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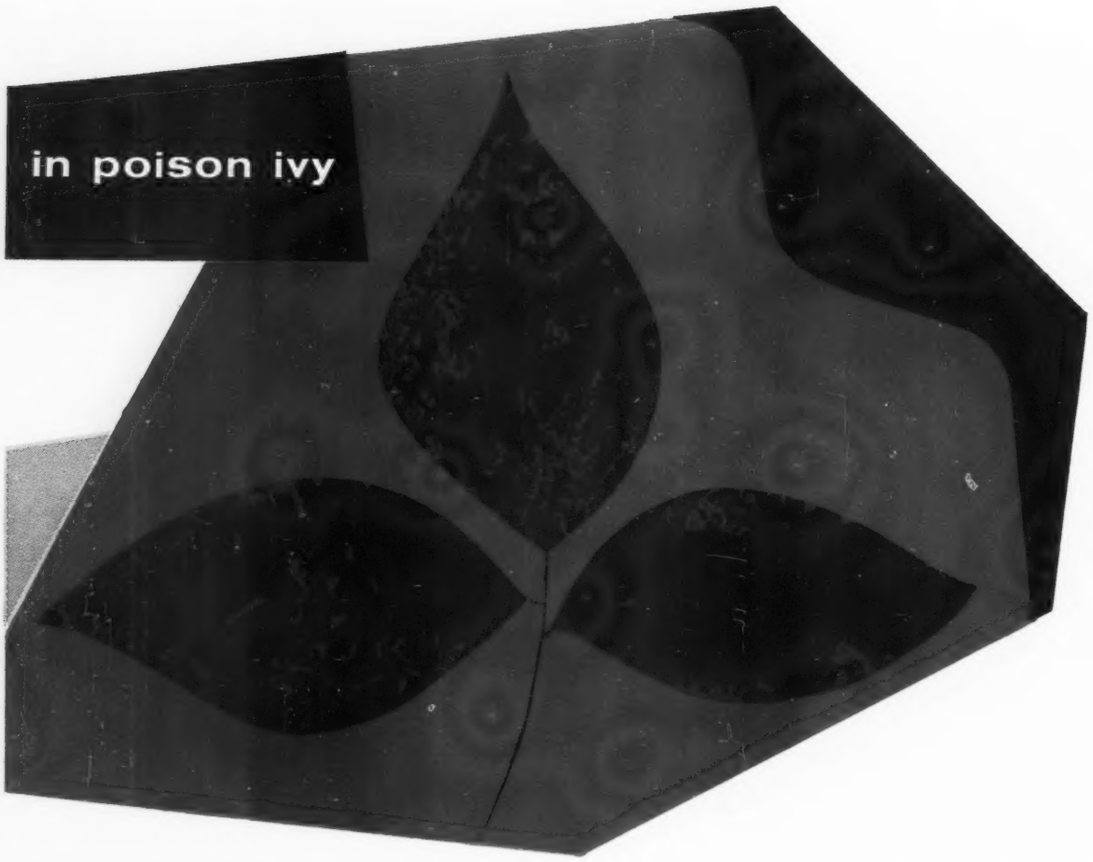

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for the patient with fever,

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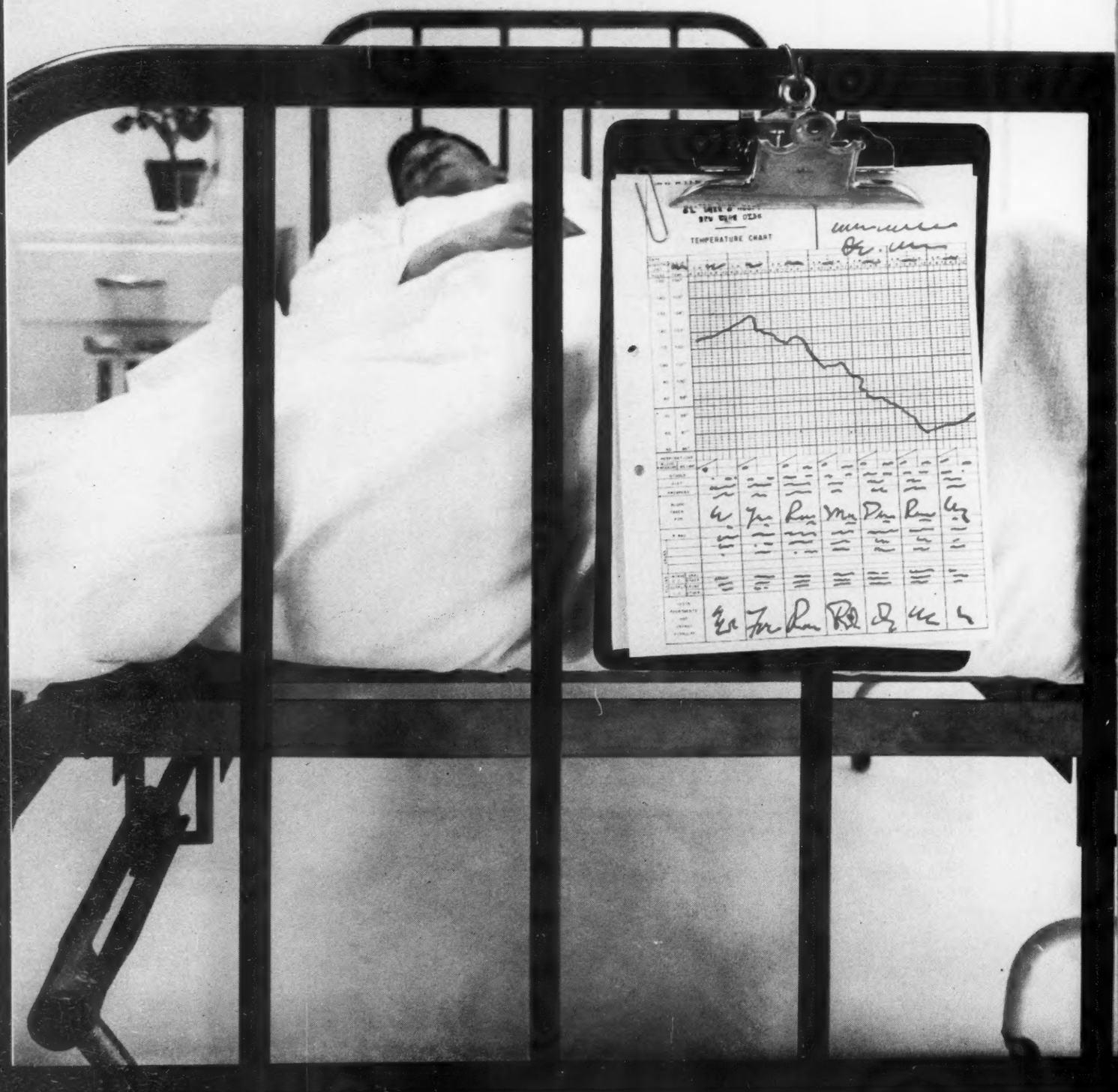

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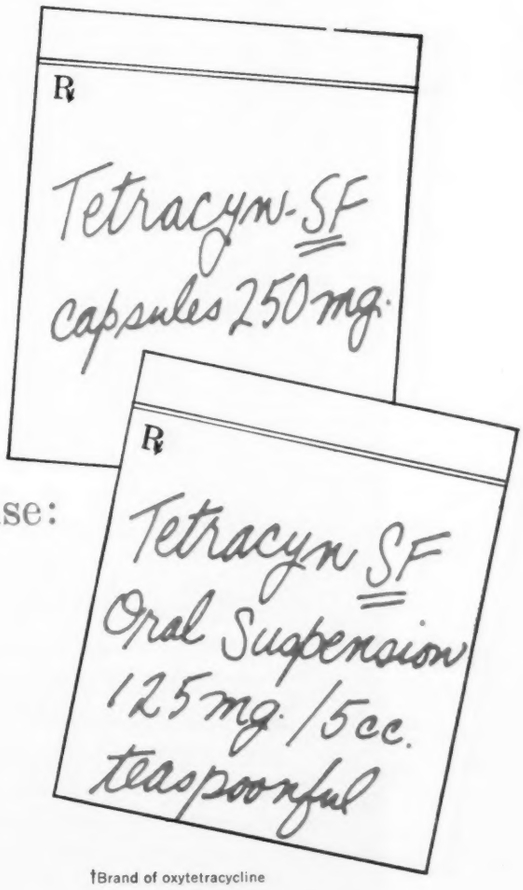

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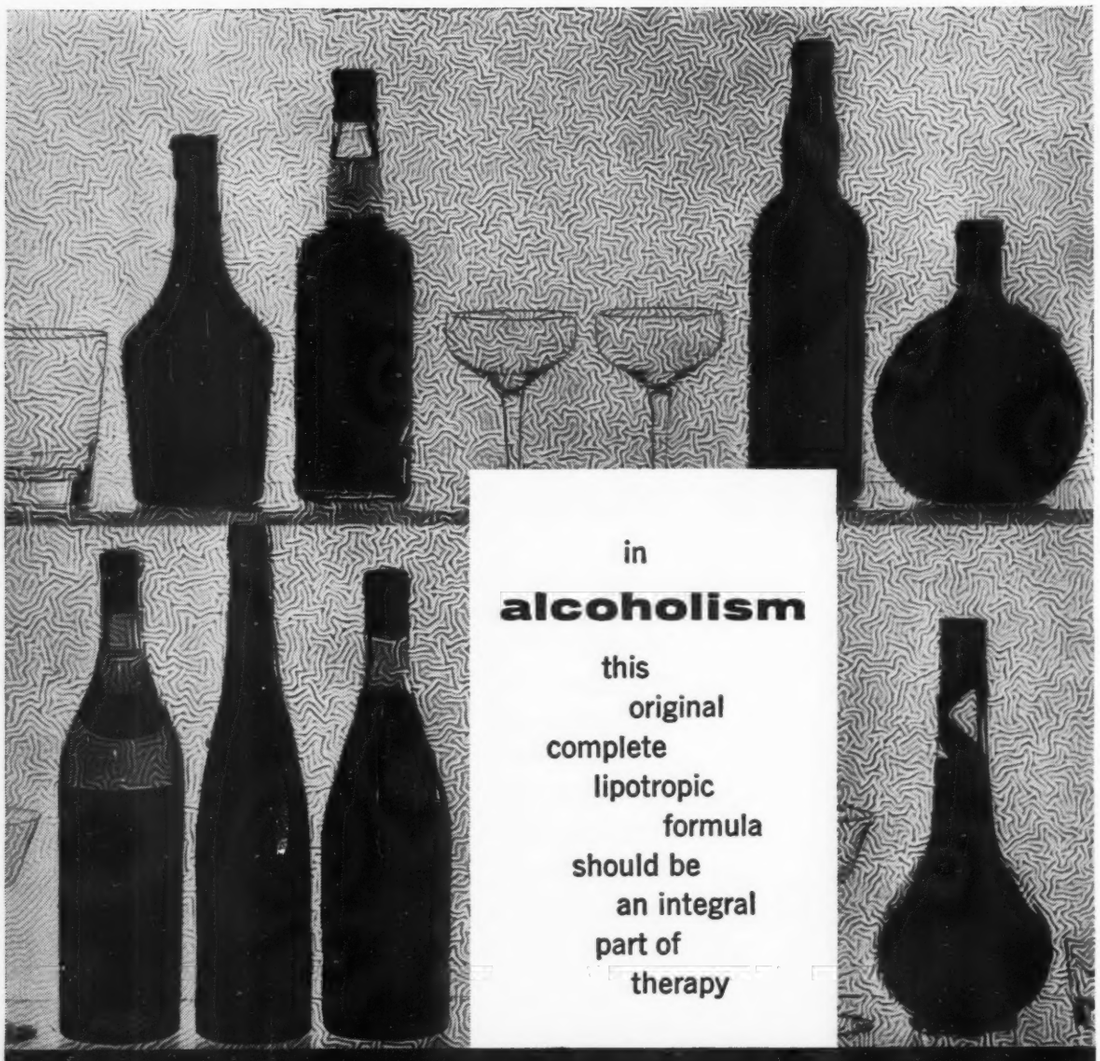

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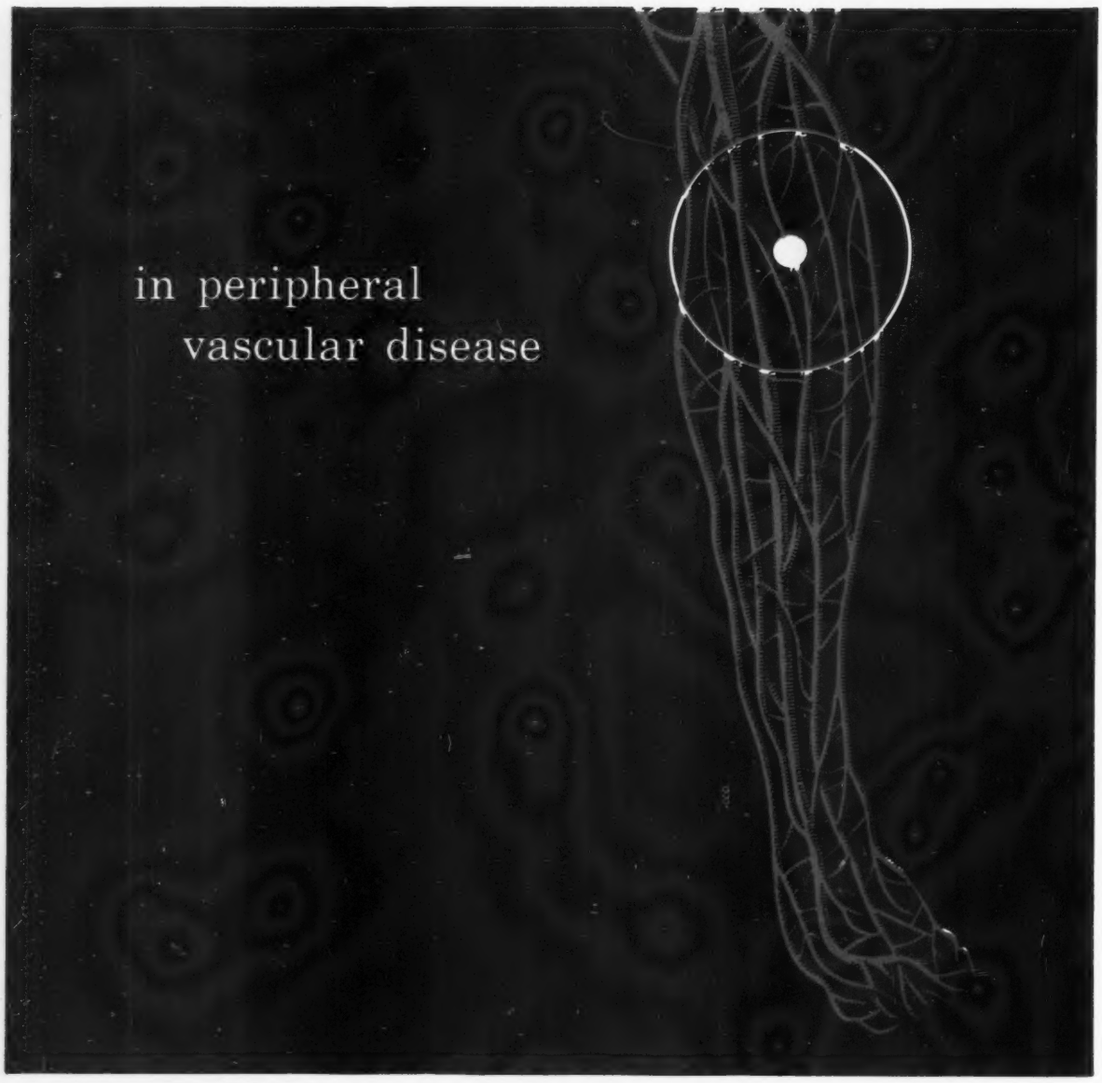

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The American Journal of Medicine

VOL. XIX AUGUST, 1955 No. 2

Editorial

Clinical Usefulness of Fructose

THE recent advances which have been made in the understanding of the metabolic processes concerned with utilization of the three hexoses mainly involved in mammalian energy metabolism, glucose, fructose and galactose, have led to renewed interest in the possible clinical usefulness of sugars other than glucose. The rediscovery of identical fructose tolerance curves in normal and diabetic subjects has more particularly directed this interest toward fructose. The potential clinical usefulness of this hexose is intimately connected with a proper understanding of the metabolic transformations involved, of the rate at which they proceed and of the differences which exist between individual tissues in these respects. A brief review of present knowledge may thus be indicated.

Metabolism of Fructose in Normal Tissues. The metabolism of fructose is schematized in Figure 1. It should be immediately pointed out that the scheme is a composite one based on studies of several tissues in several species. The reactions which are part of the usual pathways of glycolysis are indicated by heavier arrows. It is clear that whenever fructose metabolism leads to the formation of an intermediate of glycolysis, further metabolism of fructose becomes identical with that of glucose. Five reactions peculiar to fructose have been described and have been numbered in the scheme. Reference will be made later to the reactions in this scheme when individual tissues are considered.

Reaction 1: Fructose can be phosphorylated in position 6 in the presence of hexokinase and ATP. The same enzyme catalyzes the phosphorylation of glucose and mannose in the same position but its affinity is different for each of these hexoses. Competitive inhibition between these substrates has been observed. The best studied mammalian hexokinase, brain hexokinase, has a greater affinity for glucose than for fructose;[1] glucose greatly inhibits the phosphorylation of fructose by this enzyme. (Table 1.) This example alone should suffice to demonstrate the danger of drawing general conclusions from observations on the capacity of an isolated tissue to metabolize a substrate which is offered alone, without naturally present competitors.

Reaction 2: Independent investigations in St. Louis,[2] Louvain[3] and Zurich[4] have established that, in liver and muscle, fructose can be phosphorylated in position 1 by a specific fructokinase. No competitive inhibition between glucose and fructose can be demonstrated for this enzyme. Since the product of this reaction, fructose-1-phosphate, is not an intermediate of glycolysis, it must undergo further modifications before entering the standard pathways of intermediary metabolism. Direct conversion of fructose-1-phosphate to fructose-6-phosphate does not appear to occur to any significant degree.[5]

Reaction 3: Fructose-1-phosphate can be split by an enzyme closely related to aldolase[5,6] to two three-carbon fragments, of which one is phosphorylated (dihydroxyacetone phosphate) and one is not (glyceraldehyde).

Reaction 4: Glyceraldehyde can be phosphorylated by a triokinase[5] to phosphoglyceraldehyde, and the two three-carbon fragments resulting from fructose-1-phosphate are now identical with those resulting from the splitting of fructose-1-6-diphosphate by aldolase; from

this point, therefore, glucose and fructose follow the same metabolic pathways up or down the chain of glycolytic reactions.

Reaction 5: Fructose-1-phosphate can also be phosphorylated in position 6 to fructose-1-6-diphosphate.[1] Whether the enzyme involved is identical with the phosphofructokinase which catalyzes the phosphorylation of fructose-6-phosphate, is not as yet established.

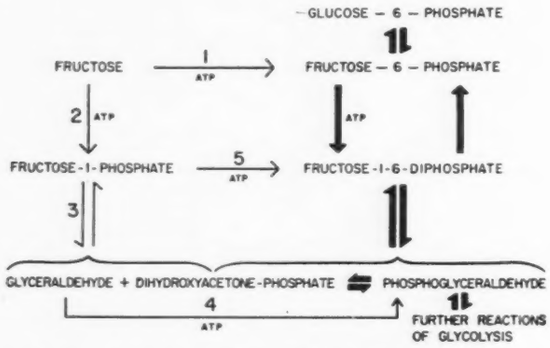

FIG. 1. Composite scheme of fructose metabolism.

When considering the metabolism of a substance to be administered to intact organisms it is important to consider not only the transformations which this substance may undergo but also the rate at which these reactions can proceed, both in the organism as a whole and particularly in each individual tissue. We shall now consider the information available on the metabolism of fructose by various tissues.

The liver is quantitatively the main site of fructose metabolism. It takes up fructose from the blood stream or from the incubation medium at a rate considerably greater than is true for glucose.[7–12] Once taken into the liver cell it is metabolized mainly by Reactions 2, 3 and 4. (Fig. 1.) The conversion of fructose to lactate, CO_2, glycogen or fatty acids exceeds that of glucose.[7,12–15] A varying portion of the fructose metabolized is transformed to glucose-6-phosphate and, by glucose-6-phosphatase action, to glucose which appears in hepatic vein blood or in the medium surrounding liver slices.[10–12] That the fructose thus rapidly metabolized yields useful energy is well exemplified by the observation of Helmreich et al.[16] who found that the capacity of the liver to produce activated two-carbon fragments capable of acetylating sulfonamide is greatly enhanced in the presence of fructose.

On the basis of data obtained by catheterization of the hepatic vein during fructose administration, Weichselbaum has estimated that up to 50 per cent of an administered fructose load is metabolized in the liver within one hour.[10] The total figure is probably considerably greater[17] since much of the fructose which had diffused into the extracellular (and probably intracellular) water later diffuses back into the blood stream to be metabolized in the liver. The ability to transform fructose to glucose is probably shared, although to a much smaller degree, by intestinal mucosa[18] and by renal tubular cells.[19]

TABLE 1
MUTUAL INHIBITION OF GLUCOSE AND FRUCTOSE PHOSPHORYLATION BY HEXOKINASE OF BRAIN[1]

Incubation Period (min.)	Initial Concentration M × 10^{-3}		Fructose Used γ	Glucose Used γ	Per cent Inhibition	
	Fructose	Glucose			Fructose	Glucose
20	2.11	0	520	...	...	..
20	0	2.38	...	375	...	..
20	2.11	2.38	0	360	100	4

While brain slices or homogenates metabolize fructose at satisfactory rates, it is doubtful whether any fructose utilization by brain occurs under physiologic conditions. This is adequately explained by the presence in the intact organism of glucose concentrations sufficient to inhibit the phosphorylation of fructose by the hexokinase of brain, as previously illustrated in Table 1. A specific fructokinase has not been found in brain. That fructose does not prevent hypoglycemic symptoms in the dog was clearly shown in 1931 by Bollman and Mann.[20] They demonstrated that in the eviscerated dog blood levels of fructose of 100 mg. per cent or more did not prevent the appearance of convulsions whenever the blood glucose level was allowed to drop below a critical level.

Whether muscle can utilize significant amounts of fructose is a matter of controversy. At best, over-all fructose utilization by muscle is slow,[21–23] proceeding at one half or less the rate of glucose utilization. Possibly it is practically non-existent,[24] as suggested by Wick who found that the rate of formation of $C^{14}O_2$ from C^{14}-labelled fructose was less than 5 per cent of that from C^{14}-labelled glucose in the eviscerated nephrectomized rabbit. Hers[17] has recently reviewed the available data, added a number of

new observations, and concluded therefrom that in the intact rat most of the fructose administered reaches striated muscle after previous conversion by the liver to glucose or to other metabolites. What fructose is directly incorporated appears mainly to follow Reaction 1. (Fig. 1.) The concept of adequate fructose utilization by muscle is based largely on measurements of fructose "uptake" by isolated tissues or of peripheral arteriovenous differences; it has been further fostered by demonstration of a specific fructokinase (Reaction 2, Fig. 1) in muscle homogenates.[1] However, studies measuring not only the uptake of fructose but also its ultimate fate in muscle tissue are more meaningful, and the situation prevailing in the intact organism, including competition with glucose, should whenever possible be preserved.

TABLE II
COMPARATIVE UTILIZATION OF C^{14}-GLUCOSE AND C^{14}-FRUCTOSE BY RAT DIAPHRAGM*

Experiment	A Glycogen Synthesized from Glucose	B Glycogen Synthesized from Fructose	Ratio A/B	C Glucose Oxidized to CO_2	D Fructose Oxidized to CO_2	Ratio C/D
	μM/gm. of tissue/90′			μM/gm. of tissue/90′		
1	7.32	1.10	6.7	4.97	1.36	3.6
2	6.64	1.13	5.9	4.22	1.20	3.5

* Both hexoses are simultaneously present in equimolar concentration (20 mM/L.) Unpublished results. Experimental conditions identical with those previously described for liver[12] and diaphragm.[27]

The incorporation of fructose and glucose carbon into glycogen and CO_2 by rat diaphragm has been compared in parallel experiments, both hexoses being present in all flasks, but only one of the two having been labeled with C^{14} in each. Results are shown in Table II and clearly indicate that in the presence of equal concentrations of glucose and fructose rat diaphragm metabolizes six to seven times more glucose than fructose in the formation of glycogen and approximately three and one-half times more glucose than fructose in the conversion to CO_2. It seems reasonable to conclude that, at best, fructose utilization by muscle is small when compared with that of glucose. Red blood cells have been shown to utilize fructose only in the absence of glucose.[22] No adequate information concerning adipose tissue has become available as yet.

Even a brief review of fructose metabolism cannot be concluded without recalling the intriguing situation present in placenta and in male accessory sexual glands.[25,26] In most species at least the early placenta and one or the other male accessory sexual gland are able to convert glucose to fructose and to secrete fructose into the embryonic blood stream or seminal fluid, respectively. Why this unique situation should have been preserved throughout evolution is at present a mystery.

Metabolism of Fructose by Abnormal Tissues. Since fructose is mainly metabolized by the liver it is not surprising that the rare anomalies of fructose utilization which have been described have been found in hepatic disease. Fructose tolerance is decreased in extensive hepatocellular damage.[27] However, more recent studies[8,15,28] using intravenous fructose tolerance tests suggest that this is a late manifestation of hepatic dysfunction and that the system responsible for hepatic fructose utilization is a resistant one. Fructosuria, an entirely benign inborn error of metabolism associated with a marked decrease in fructose tolerance,[29] quite likely results from deficient hepatic fructokinase activity, although this has not been conclusively established. The metabolism of fructose in diabetes mellitus has been repeatedly studied. It has been postulated, since Minkowski's demonstration of glycogen formation from fructose in pancreatectomized dogs,[30] that diabetic tissues utilize fructose at nearly a normal rate. This has since been further substantiated both in the intact organism[9,15,31] and in isolated liver tissue;[12,14] it indicates that at least the Reactions 2, 3 and 4 (Fig. 1) are not dependent on the presence of insulin. The small portion of fructose, however, which is metabolized by way of hexokinase (Reaction 1, Fig. 1) may be influenced by insulin.[17,32] That the latter observation is of little quantitative significance is suggested by the well established normal fructose tolerance in the diabetic organism. On the other hand, it should be clearly understood that the presence of normal fructose tolerance in diabetes suggests no more than that the diabetic tissues utilize fructose as well or, for certain tissues, as poorly as normal tissues. It evidently does not justify the assumption that tissues such as brain or muscle, which utilize little or no fructose in the normal situa-

tion, utilize fructose any better in the presence of diabetes.

POTENTIAL CLINICAL USEFULNESS

It would seem reasonable to expect that significant clinical advantage could be derived from several of the unique physiologic properties of fructose.

1. The almost exclusive utilization by hepatic tissue, the presence of a separate, specific and quite resistant set of hepatic enzymes for its disposal, and the rate of hepatic fructose uptake suggest its use as a carbohydrate source in liver disease. Thus when fructose is administered intravenously a much larger portion of the administered carbohydrate may be expected to enter the liver cells than in the case of glucose. This may well explain the relatively greater protein-sparing effect of fructose which has been described[33] and the favorable effect of fructose on some hepatic detoxifying processes, such as the striking effect in acute ethanolic intoxication.[34]

2. The rapidity of hepatic fructose uptake indicates its use as a substitute for glucose whenever glucose must be administered rapidly and whenever the renal threshold for glucose is exceeded, leading to glucose wastage and to the concomitant undesirable osmotic diuresis. Although the renal threshold for fructose is lower than that for glucose the rapid fall in blood fructose levels minimizes the amount of fructose lost in the urine. In the presence of untreated diabetes mellitus the markedly decreased glucose tolerance contrasts even more with the intact tolerance for fructose. Thus the addition of 2 or 5 per cent fructose to hypotonic balanced electrolyte solutions used during the initial treatment of diabetic acidosis has been suggested.[35] A much smaller portion of the carbohydrate thus administered is wasted in the urine than would be true for glucose.

3. A further rationale for the use of fructose during the first hours of treatment of diabetic acidosis should be mentioned. While glucose uptake by diabetic liver is markedly impaired,[36] direct effects of insulin on hepatic tissue have not been well established. In the rat it has been clearly demonstrated[37] that several hours elapse before insulin administration affects the deranged intermediary metabolism of the diabetic liver. Fructose, which can be immediately utilized by diabetic liver, may thus represent an emergency carbohydrate supplement.

4. Present knowledge does not permit a decision as to whether or not fructose has anything to offer when used as an adjunct in the long-term therapy of diabetes mellitus. It is difficult, however, to dismiss the thought that, since perfect control of diabetes with insulin throughout the twenty-four hour period is rarely achieved, fructose, representing a ready source of insulin-independent carbohydrate for the liver, might supply the liver with necessary carbohydrate molecules during daily periods of relative insulin deficiency. Whether this could contribute, for instance, to control of the anomalies of lipid metabolism in the diabetic liver is a question deserving some consideration. Certainly it would appear from recent trials in man[38] as well as in rats[39,40] that a somewhat greater portion of administered fructose is retained than is the case for glucose. It had previously been suggested that with prolonged periods of administration more and more fructose would be lost as glucose. These recent observations, however, do not appear to support this suggestion.

5. Finally, it should be mentioned that the rapid and almost exclusive hepatic utilization of fructose may be used to assess the functional state of the liver at any given moment by presenting it with a fructose load and by measuring the relative rates of appearance of various groups of its metabolites. Similarly, it has been shown in liver slices that although normal and diabetic tissue utilize fructose at the same overall rate, incorporation of fructose into different metabolites varies greatly with the metabolic situation encountered.[12]

POTENTIAL CLINICAL DANGERS

Certain potential clinical dangers should not be forgotten. First, whenever fructose is administered in large amounts the assumption is made that the liver will transform a sufficient amount of fructose into glucose in order to supply the needs of tissues such as brain and muscle which cannot use fructose directly in sufficient amounts. This assumption is not always justified. For instance, in patients receiving insulin the peripheral rate of glucose removal from the blood stream may exceed the rate of glucose formation from fructose, and hypoglycemia may develop. This may go unrecognized since routine methods for blood glucose measure fructose as well. Further difficulties may result from the excessive rate

at which fructose is metabolized when given intravenously in large amounts. Sufficient amounts of lactate and pyruvate may accumulate to produce significant acidosis. Also, in the treatment of diabetic acidosis glycogen deposition from fructose may be rapid enough to accentuate greatly any tendency to hypokalemia. Finally, it should be stressed that the administration of fructose in diabetic acidosis should never be considered to alter in any way the insulin requirement or the need for speed in reaching adequate control with insulin.

SUMMARY AND CONCLUSION

The metabolism of fructose has recently been greatly clarified and has been found to differ considerably from that of glucose. The main features of this difference are the almost exclusive utilization of fructose by liver, the presence of separate specific enzymes for its disposal, the rate of its uptake by hepatic tissue and the lack of any significant dependence of this rate on the presence of insulin. The abundant literature concerning its clinical usefulness which has accumulated over the past fifty years yields no conclusive answer. A fresh appraisal of the potential clinical usefulness of fructose in the light of new knowledge concerning its physiologic properties is clearly indicated.

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Clinical Studies

Precipitation of Ventricular Arrhythmias Due to Digitalis by Carbohydrate Administration*

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THE clinical studies of Sampson et al.[1] demonstrating the abolition of digitalis-induced ventricular arrhythmias by administration of potassium salts have been recently reinvestigated by Lown and coworkers,[2] and the relationship of digitalis intoxication to potassium metabolism has been extensively reviewed by Lown and Levine.[3,4] The latter were able to confirm Sampson's findings and in addition to establish that potassium depletion predisposes to the development of cardiac manifestations of digitalis toxicity and enhances arrhythmias already present. The so-called "postmercurial redigitalization phenomenon," the arrhythmias occurring in digitalized patients during therapy with adrenal steroids, and the similar cardiac disturbances in digitalized subjects sustaining large losses of gastrointestinal fluids were all shown to have a potassium deficit as their common denominator. Although no reliable correlation was found between sensitivity to digitalis and the serum potassium concentration, a reciprocal relationship was thought to exist between total body potassium and sensitivity to the foxglove: the tendency to cardiac arrhythmias during digitalis therapy was increased by potassium depletion, and the arrhythmias in turn were abolished by correction of the potassium deficit.

The occurrence postprandially of electrocardiographic changes resembling those of potassium deficiency (T wave depression, appearance of prominent U waves) with or without a fall in serum potassium levels has been described by Rochlin and Edwards.[5] These workers implicated dietary carbohydrate as responsible for the changes found. They suggested that the electrocardiographic or chemical evidence for a lowered potassium results from the entry of potassium with carbohydrate into liver and muscle cells, presumably through a mechanism involving endogenous insulin.

The demonstration of carbohydrate-induced hypopotassemia or of changes resembling potassium depletion, together with the now well documented aggravation of digitalis toxicity by potassium deficiency, suggested that a relationship might exist between carbohydrate metabolism and clinical digitalis intoxication. The following study will report seven patients in whom ventricular arrhythmias were apparently precipitated by orally or intravenously administered carbohydrate while they were being treated with digitalis glycosides.

METHODS

Patients who were receiving digitalis therapy or presented problems of special interest in digitalis intoxication were selected from the ward service of the Jefferson-Hillman Hospital. Thirty-seven patients were investigated a total of ninety-nine times. With the exception of J. T., who was followed as an outpatient, all patients were studied in the basal, fasting state at about 6:30 A.M. Continuous control electrocardiograms were taken for a three- to five-minute period. One hundred grams of glucose in water were then given orally in five minutes, and serial three-minute strips of electrocardiograms (using a Sanborn Viso-Cardiette) were taken at five- to fifteen-minute intervals for a period of from thirty to 120 minutes. Intravenous admin-

* From the Department of Medicine, Medical College of Alabama, Birmingham, Ala. Aided by a grant from The Life Insurance Medical Research Fund.

istration of 50 cc. of 50 per cent glucose in water or of 200 to 400 cc. of 10 per cent glucose in water, or the eating of an ordinary high carbohydrate (low-salt) breakfast, were occasionally substituted for the test dose of oral glucose. The observer was present throughout the test to insure that subjects remained quiet, the usual result being that patients fell asleep during the procedure. Whenever possible, patients were studied repeatedly on successive days following stepwise increases in their digitalis dosage. No systematic attempt was made to follow serum potassium levels.

RESULTS

Of the thirty-seven patients in the group studied, ventricular arrhythmias attributable to carbohydrate administration were demonstrated in seven. Ventricular arrhythmias were precipitated on ten occasions after ingestion of 100 gm. of glucose by mouth, on three occasions after a high carbohydrate meal, once after rapid injection of 50 cc. 50 per cent glucose in water intravenously and once after slower infusion of 10 per cent glucose in water. Identical changes were produced by intravenously administered glucose and by a high carbohydrate meal in one patient; another patient demonstrated the same changes after oral glucose as after a high carbohydrate meal.

At the time of the procedure, five of the patients manifested either nausea or ventricular arrhythmias not present before digitalis therapy and would therefore, by the classic criteria, have been considered to show overt digitalis intoxication. In two patients the manifestations of toxicity, as reflected by ventricular premature beats, were evident only after administration of carbohydrate; both of these men had exhibited these arrhythmias in clear relationship to their digitalis therapy on previous days, although they were not considered on clinical grounds to exhibit digitalis toxicity at the time of the test. Of the thirty patients in whom carbohydrate administration failed to elicit disturbances of rhythm, digitalis intoxication was suspected on clinical grounds in only three. Two of these had ventricular premature beats not present before digitalis therapy; the third showed electrocardiographic evidence of auricular tachycardia with block developing while his digitalis dosage was being rapidly increased. Three patients in whom the test procedure induced arrhythmias were receiving 6 gm. or more of potassium chloride daily by mouth. None of these had taken potassium for at least eight hours before carbohydrate administration.

CASE REPORTS

Case I. (Hospital No. 15942.) W. R., a fifty-nine year old man, was admitted with a history of exertional dyspnea and edema of three years' duration. Hypertension was known to have been present at least one year. The patient had received 0.1 gm. digitalis folia daily for the past twelve months. In the week preceding admission, as an outpatient, he was given four mercurial injections, supplemented by 0.3 gm. potassium chloride three times daily. There were no symptoms of digitalis intoxication.

The electrocardiogram showed only first degree heart block and non-specific T wave changes. A control tracing revealed one premature beat in five minutes. Sixteen minutes after oral administration of 100 gm. of glucose the tracing showed coupled, occasionally repetitive and multiform premature beats (Figs. 1A and B) with a frequency of twelve per minute, which were still present fifty-five minutes later. Similar results were obtained after oral glucose on three additional occasions, on which it was further noted that, while no premature beats could be demonstrated immediately after ingestion of glucose, bigeminy would invariably appear between fifteen and twenty minutes after such feedings.

To test the effect of an ordinary meal the patient was studied before and after an ordinary low-salt breakfast consisting of scrambled eggs, two pieces of toast, and weak coffee with a double serving of sugar. A five-minute control cardiogram and a three-minute strip immediately after eating showed no premature beats. Fifteen minutes after the end of the meal bigeminal beats were first apparent, increasing to a frequency of 5 per minute thirty minutes postprandially (Fig. 2) and still present after one hour.

Case II. (Hospital No. C35198.) J. H., a fifty-five year old man, was admitted with a history of angina pectoris for nine months, and edema, dyspnea and orthopnea for three weeks prior to entry. Physical examination revealed a blood pressure of 130/90 and pulse of 85. The patient was a chronically ill appearing male with Cheyne-Stokes respirations, rales at both lung bases, hepatomegaly, and the thickened skin of chronic edema over his lower legs. The

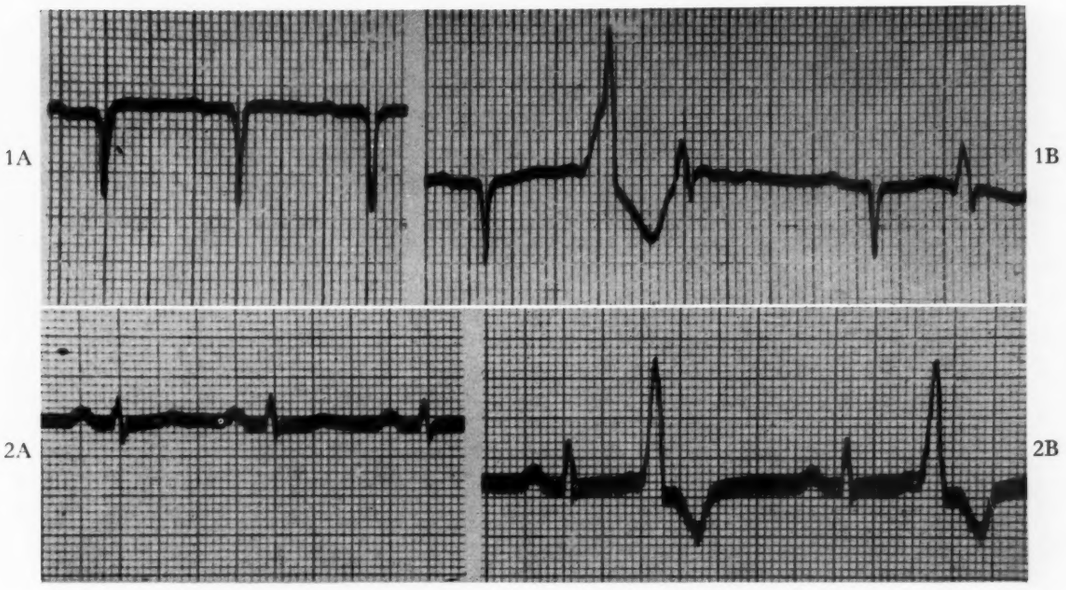

FIG. 1. Case I. (Lead III.) A, control tracing before oral glucose showed only one premature beat in five minutes. B, sixteen minutes after 100 gm. glucose by mouth; note numerous bigeminal, multiform, occasionally repetitive premature beats.

FIG. 2. Case I. (Lead II.) A, control tracing before breakfast; no premature beats in five minutes. B, thirty minutes after breakfast; note appearance of bigeminy.

heart was enlarged to the anterior axillary line with a localized, expansile apical impulse, accentuated P2, diastolic gallop, and a grade I decrescendo early diastolic murmur along the left sternal border. Admission laboratory data included a serum potassium of 5.3 mEq./L., serum sodium of 145 mEq./L. The patient received 1.7 gm. digitalis folia over a nine-day period, and was given occasional mercurial injections, and a daily dose of ammonium chloride, 4 gm. per day. There were no symptoms of digitalis toxicity.

The electrocardiogram was suggestive of left ventricular hypertrophy and digitalis effect. A control tracing revealed multiform ventricular premature beats with a frequency of only two per minute. (Fig. 3A.) Five minutes after ingestion of 100 gm. of glucose the T waves became inverted. At thirty minutes the frequency of premature beats had increased to eight per minute. Forty minutes after ingestion of glucose there was marked cardiac slowing and the electrocardiogram showed the classic changes described in potassium deficiency, with prolongation of the P-R interval, inverted T waves, and prominent positive after-potential ("U waves"). (Fig. 3B.) Concomitantly, the frequency of premature beats increased to twelve per minute, the coupled premature beats appearing to interrupt the U wave. (Fig. 3C.) Repetition of this test on two additional days yielded essentially similar results.

CASE III. (Hospital No. A93439.) W. B. S., a sixty-six year old man, was admitted with a history of dyspnea of seventeen months' duration, and of edema and nocturnal dyspnea of three months' duration. Although he was known to be subject to bouts of "paroxysmal tachycardia," he had not been digitalized because of alleged "digitalis sensitivity." Physical examination revealed a blood pressure of 140/90 mm. Hg and a pulse of 95–100 per minute. The patient was a somewhat wasted, emphysematous man with distended neck veins, rales at both lung bases and hepatomegaly. The heart was questionably enlarged and, except for an irregular rate, was not otherwise remarkable.

Admission electrocardiogram (before digitalis) was suggestive of left ventricular hypertrophy and revealed ventricular premature beats from the same focus (Fig. 4A), often appearing as a trigeminal rhythm. It was found difficult to digitalize the patient because of a tendency to develop a bizarre, presumably ventricular tachycardia. He was finally given a total of 3.5 mg. gitaligen® over a three-day period and potassium chloride 6 gm. per day.

Electrocardiograms before and five minutes

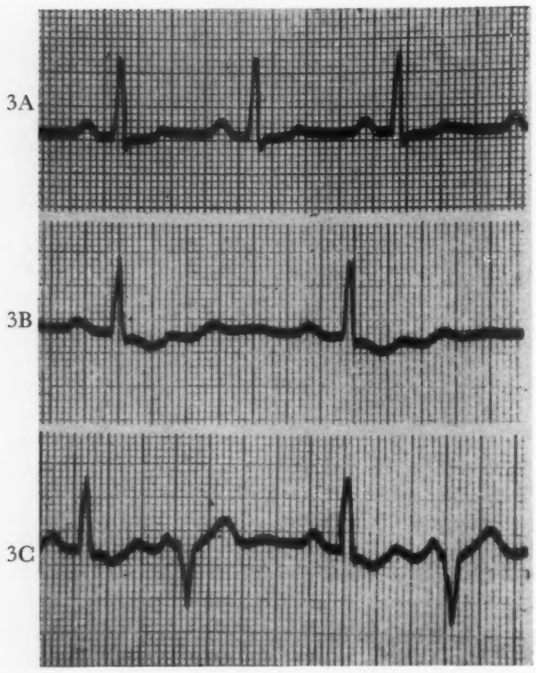

FIG. 3. Case II. (Lead II.) A, control tracing. B and C, strips from different parts of tracing taken forty minutes after 100 gm. glucose by mouth; note prolonged P-R interval, T wave changes and prominent "U waves" in B which are interrupted by coupled premature beats in C.

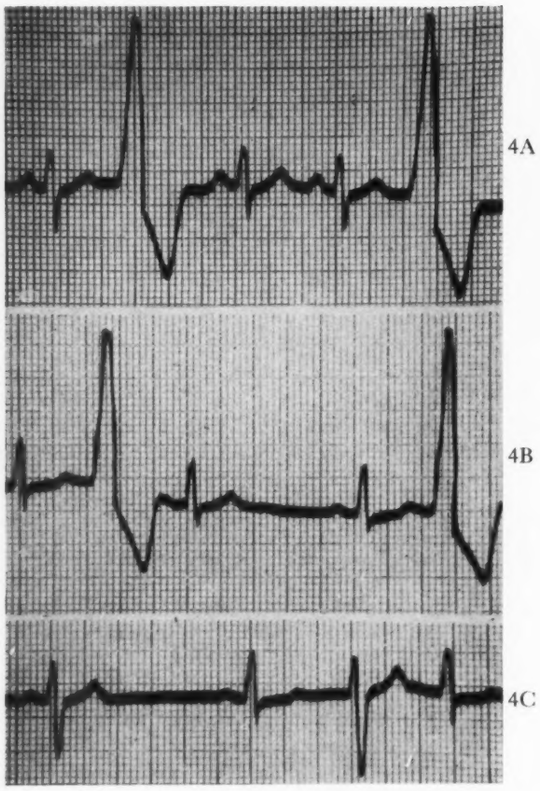

FIG. 4. Case III. (Lead II.) A, control, before digitalization. B, control before glucose, after digitalization; note persistence of bigeminal beats present before digitalis. C, twenty minutes after intravenous injection of 50 ml. of 50 per cent glucose in water; note replacement of previous bigeminy by ectopic beats of different configuration.

after intravenous injection of 50 cc. of 50 per cent glucose in water showed only the premature beats which had been noted prior to digitalization. (Fig. 4B.) Ten minutes after the injection the previously described premature beats were noted virtually to disappear, to be replaced by complexes from a new ectopic focus with a frequency of fifteen per minute (Fig. 4C) which persisted for forty-five minutes. In the subsequent twenty-four hours the patient received an additional 1.5 mg. of gitaligen. The next morning tracings taken before and immediately after breakfast (consisting of grapefruit juice, cereal with sugar, one egg and weak coffee with sugar) again showed only the single focus of premature beats that had been present before digitalization. Fifteen minutes postprandially the new ectopic focus previously elicited with intravenous glucose reappeared, reaching a maximum frequency of 16 per minute one-half hour after the meal, and again completely replacing the other focus.

CASE IV. (Hospital No. C35354.) H. H., a forty-eight year old man with known luetic aortic insufficiency, had been followed in the outpatient department over a six-month period on maintenance doses of digitalis, multiple mercurial injections, oral mercurials and carbonic acid anhydrase inhibitor. Two weeks prior to admission, on a visit to the emergency ward, he had inadvertently received a second complete digitalizing dose of digitalis leaf while continuing his maintenance dose of the drug and the mercurial diuretic therapy. On this regimen he had developed increasing edema and dyspnea and on admission had been vomiting for several days. Physical examination revealed a cachectic, orthopneic man with a blood pressure of 130/80 mm. Hg, distended neck veins, hepatomegaly and edema. The heart was diffusely enlarged to the right and left, the heart sounds tumultous with a rapid rate alternating with runs of slower bigeminal rhythm. Admission electrocardiogram revealed complete atrioventricular dissociation with multiform, coupled ventricular complexes and runs of multidirectional ventricular tachycardia at a rate of 150 beats per minute. An intravenous infusion of 5 per cent glucose with 40 mEq. potassium chloride

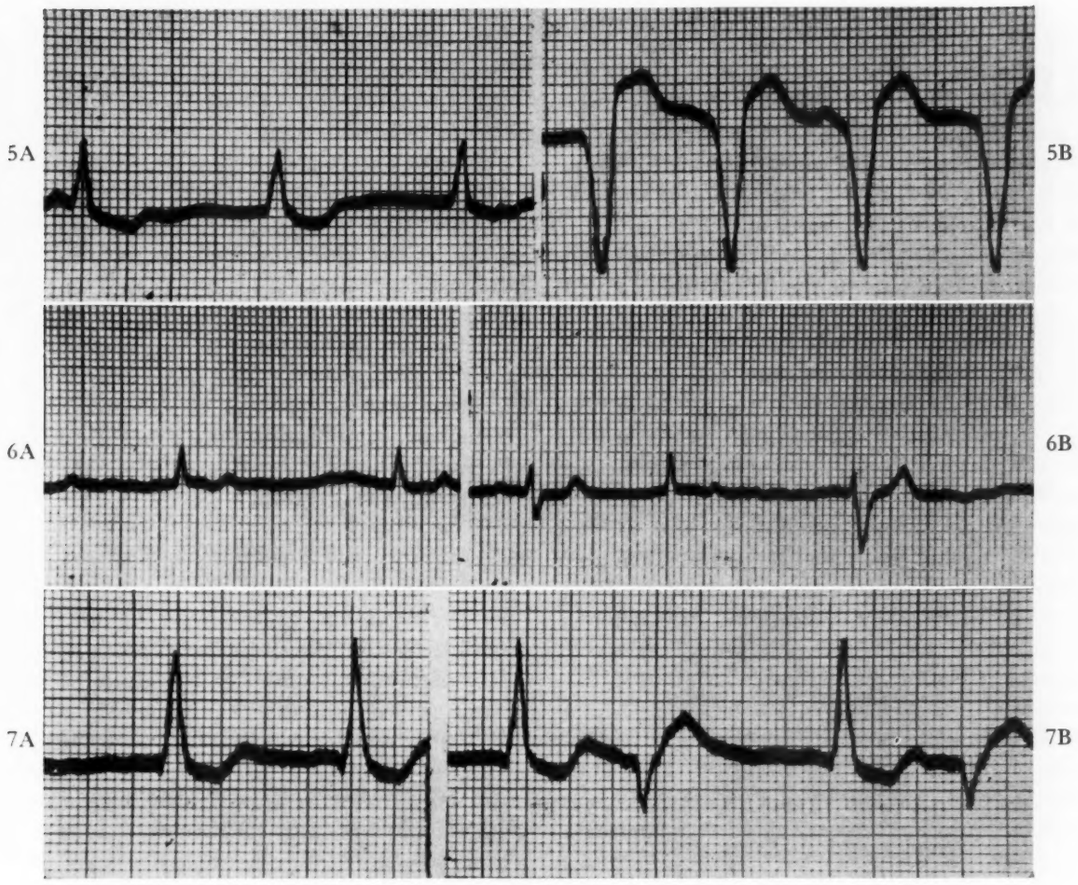

FIG. 5. Case IV. (Lead II.) A, control tracing showing complete A-V dissociation with normal ventricular complexes. B, twenty minutes after breakfast; note appearance of ventricular tachycardia.

FIG. 6. Case V. (Lead I.) A, control tracing showing only slow auricular fibrillation. B, fifteen minutes after start of infusion of 10 per cent glucose in water; note appearance of ventricular ectopic beats.

FIG. 7. Case VI. (Lead aVL.) A, control tracing shows no premature beats. B, forty-five minutes after 100 gm. glucose by mouth; note appearance of bigeminy.

promptly abolished the ventricular tachycardia and bigeminal beats, and reverted the configuration of the ventricular complexes to what it had been prior to the present episode. Termination of the infusion resulted in rapid recurrence of the chaotic ventricular rhythm. Accordingly, the patient was given procaine amide, 0.5 gm. every four hours by mouth, and potassium chloride, 2.0 gm. every eight hours. Thirty-six hours later a three-minute control tracing taken before breakfast revealed no abnormal ventricular complexes, although complete A-V dissociation persisted. (Fig. 5A.) The patient was then given breakfast consisting of toast, cereal with a double serving of sugar, eggs and weak coffee with sugar, taken over a half-hour period. A tracing taken five minutes after breakfast showed one premature beat in three minutes. Twenty minutes postprandially there appeared a one and one-half minute run of ventricular tachycardia at a rate of 110 per minute. (Fig. 5B.) Potassium and procaine amide therapy was continued for the next twenty-four hours. Feeding of 100 gm. of glucose the following morning failed to elicit abnormal ventricular complexes.

CASE V. (Hospital No. C42179.) C. P., a twenty-three year old man with rheumatic heart disease and congestive heart failure of long-standing, was admitted because of progressive dyspnea. Physical examination revealed cardiomegaly, auricular fibrillation, and murmurs of mitral stenosis, aortic stenosis and aortic insufficiency. An electrocardiogram showed auricular fibrillation, left ventricular hypertrophy and occasional ventricular premature

beats. These ventricular premature beats disappeared during intensified digitalis therapy. Two tests, on successive days, with 100 gm. glucose orally failed to elicit any arrhythmias after 1.6 gm. digitalis folia and 1.0 mg. digoxin, respectively. On the fifth day of digitalis therapy, having had a total of 2.2 gm. digitalis, the patient for the first time complained of nausea. Attempts at oral glucose feeding were aborted by retching. The patient was accordingly given an infusion of 10 per cent glucose in water at 15 cc. per minute. Control electrocardiogram (Fig. 6A) showed no abnormal ventricular complexes. The ventricular rate remained at seventy per minute throughout the infusion. Fifteen minutes after the start of the intravenous drip, tracings indicated multiple repetitive ventricular premature beats (Fig. 6B) (alternatively, a slightly irregular idioventricular pacemaker). Five hours later, when the patient's nausea had completely subsided, intravenous injection of 40 cc. of 50 per cent glucose in water failed to elicit abnormal ventricular complexes.

Case vi. (Hospital No. C21863.) L. M., a forty-six year old man with luetic aortic insufficiency, long-standing hypertension and congestive failure of four years' duration, was admitted because of increasing edema, anorexia and nausea. He had received 1.4 gm. of digitalis folia over a five-day period in addition to his previous maintenance dose. Physical examination revealed a blood pressure of 210/140 mm. Hg, marked wasting, pulmonary congestion, hepatomegaly, edema, marked cardiomegaly, and a grade iv aortic decrescendo diastolic blowing murmur. In spite of marked nausea the patient was able to retain 100 gm. of glucose by mouth. Control electrocardiogram showed auricular fibrillation, left ventricular hypertrophy and intraventricular block, but revealed no premature beats. (Fig. 7A.) Thirty minutes after glucose ingestion rare bigeminal beats appeared, and at forty-five minutes runs of classic coupling were in evidence. (Fig. 7B.)

Case vii. (Hospital No. 53054.) J. T., a seventy year old man with known hypertension for six years, was seen as an outpatient with complaints of nocturnal dyspnea and edema of six weeks' and one month's duration, respectively. Physical examination revealed an obese, emphysematous man with a blood pressure of 220/130 mm. Hg, distended neck veins, signs of fluid at the right lung base, dependent edema and moderate cardiomegaly. An electrocardiogram prior to digitalization showed first degree heart block and was suggestive of left ventricular hypertrophy. There were no premature beats. The patient received 1.2 gm. digitalis folia over a twenty-four-hour period. Following this he had a diuresis and diarrhea (seven stools in one day) developed. He was seen again thirty hours after the last dose of digitalis. Control electrocardiogram at this time revealed increase in his first degree heart block with occasional 2:1 second degree block. In addition, rare multiform ventricular premature beats had developed with a frequency of two per minute. Fifteen minutes after an oral dose of 100 gm. glucose the premature beats had become repetitive and more frequent, attaining a maximal frequency of fifteen per minute at one hour.

DISCUSSION

Clinical Implications. The precipitation of fatal ventricular arrhythmias is the cardinal hazard of digitalis therapy. Frequently the appearance of ventricular extrasystoles heralds the onset of an ominous sequence which, in the presence of the underlying structural heart disease, progresses to ventricular tachycardia and culminates in ventricular fibrillation. The demonstration that such arrhythmias can be brought out or aggravated by oral or intravenous carbohydrate administration is therefore of some importance. This is true in the patient nauseated from digitalis overdosage, in whom infusions of glucose in water are often the principal means of sustaining adequate nutrition while nausea and vomiting persist. It applies equally to the decompensated patient with a recent myocardial infarction (or some other cause of an "irritable myocardium") in whom the delicate balance may be upset in favor of ventricular fibrillation by a digitalis-induced ectopic rhythm.

If it is true that the arrhythmias described here represent aggravation of digitalis toxicity as a result of a fall in the plasma potassium secondary to fluctuations in the blood sugar level, clinical judgment might suggest the advisability of certain precautionary steps. Prophylactic administration of potassium salts with oral or intravenous carbohydrate, and avoidance of excessive blood sugar fluctuations by restricting highly refined carbohydrate in the diet would seem logical measures; it must be emphasized that no evidence for their efficacy is available from this study. In this regard, the

management of digitalis intoxication resembles that of periodic familial paralysis,[6] since in both conditions ventricular arrhythmias on the one hand, and muscular paralysis on the other, can be precipitated by a carbohydrate-induced serum potassium fall and can be prevented by potassium therapy. In view of the fact that both epinephrine and insulin have been shown to cause a marked fall in blood potassium levels,[7,8] one may speculate further on the importance of suppressing excessive emotional discharges and spontaneous hypoglycemia in critically digitalized patients.

Mechanism. Lown and associates were able to produce ventricular ectopic beats and ventricular tachycardia by the selective removal of potassium from digitalized dogs[9] and patients,[3] using the artificial kidney. In addition, they reported a patient in whom digitalis intoxication was evoked after lowering the serum potassium from 4.1 mEq./L. to 3.0 mEq./L. following administration of 50 gm. glucose with 25 units of insulin, the arrhythmia being abolished by a single oral dose of potassium acetate.[2] These data, in conjunction with their similar findings in potassium depletion associated with mercurial diuresis, gastrointestinal potassium loss and adrenal steroid therapy, have established that a fall in serum potassium or potassium depletion may bring out toxic cardiac manifestation due to digitalis in digitalized subjects.

In 1924 Harrop and Benedict[10] first demonstrated the fall in plasma potassium levels after oral glucose feeding of non-diabetics. Farber et al.,[8] who recently restudied this phenomenon, were able to show a consistent fall in *arterial* plasma potassium levels after oral or intravenous glucose, and emphasized the failure of the *venous* plasma potassium levels to reflect the changes detected in arterial blood. The latter finding may explain why Rochlin et al.,[5] who determined postprandial potassium levels in venous blood, were often unable to correlate the electrocardiographic changes suggestive of hypopotassemia with a simultaneous fall in potassium. That these electrocardiographic changes are clearly related to hypopotassemia was demonstrated by Parrish, Sugar and Fazekas,[11] who were able to reverse the T wave inversion and Q-T prolongation during insulin-induced hypoglycemia and hypopotassemia by administering potassium, without, at the same time, correcting the hypoglycemia. Moreover, the terms "postprandial T wave inversion, prolonged Q-T interval, and appearance of U waves" are probably inaccurate, since all of these electrocardiographic phenomena are said to represent interference with the T or U wave by a positive after-potential which is distinct from the T and U waves and which may be abolished by potassium administration.[12,13] There is good evidence[14] relating the plasma potassium fall to the entry of potassium into hepatic parenchymal cells during deposition of liver glycogen. Experiments *in vitro* on potassium entry into muscle during glucose deposition have yielded discordant results,[15–17] and studies in man[8] were interpreted by Farber et al. as pointing to a loss of potassium by peripheral tissues in an effort to maintain the plasma level. Whatever the mechanism, the arterial plasma potassium does fall. There is some question as to whether the electrocardiographic changes resembling those of potassium depletion are a reflection of the lowered level in the arterial plasma or of a total body potassium deficit. In the latter case, one would have to postulate that, in entering the cells with carbohydrate, potassium temporarily enters a "compartment" which is not functionally a part of ionically active body potassium.

An alternative explanation for the fall in plasma potassium would be to link it to the extracellular alkalosis of the postprandial "alkaline tide." This explanation receives some support from the demonstration by Magida and Roberts[18] that the electrocardiogram in alkalosis is indistinguishable from that of hypopotassemia, and from the finding by Darrow and others[19] that alkalosis tends to be associated with potassium depletion. Operation of this mechanism in precipitating digitalis intoxication by its potassium-lowering effect cannot be ruled out in those patients in this series manifesting toxicity after an ordinary meal, but seems unlikely after oral glucose alone, and is not applicable to those instances in which intravenous glucose was used. Similarly, an attempt to explain carbohydrate-induced ventricular arrhythmias in digitalized patients on the basis of the extra demands made on the circulatory reserve by the digestive processes fails to account for the response to intravenous glucose and would not explain why this reaction was found only in patients at or near the point of digitalis intoxication. All thirty-seven patients in the group studied had heart disease of comparable severity; in fact, while the seven patients with positive responses are still living, there have

been five deaths in the thirty patients in whom carbohydrate failed to induce ventricular arrhythmias.

SUMMARY

Administration of carbohydrate orally or intravenously in seven patients at or near the point of digitalis intoxication precipitated ventricular premature beats in six patients and ventricular tachycardia in one patient.

This effect is attributed to reduction in the arterial plasma potassium level after carbohydrate administration.

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The Efficacy of Carotid Sinus Pressure in the Differential Diagnosis of Triple Rhythms*

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THE accurate diagnosis of heart disease depends to a considerable extent upon the art of auscultation first described over 2,000 years ago by Hippocrates;[1] brought into sharp focus with the introduction of the stethoscope by Laennec in 1819;[2] first graphically recorded by Huerthle[3] in 1893; its basic laws defined by Rappaport and Sprague[4,5] in 1941–1942; and owing many of its present achievements to the important contributions of Levine,[6,7] Wolferth and Margolies,[8] Evans,[9,10] Lian,[11] Luisada[12] and others.[13–18]

Normally, the contraction and relaxation of the heart produces two sounds; occasionally, three. These are predominantly valvular in origin, the energy of the first sound being derived primarily from vibrations set up by the closure of the A-V valves and that of the second sound from vibrations subsequent to the closure of the semilunar valves. Muscular and vascular movements also contribute to these sounds so that the graphic record of each sound can actually be divided into four component parts on the basis of their derivation. In conditions which alter the valves, vibrations result which have been termed murmurs and whose significance and clinical interpretation forms an integral part of the art of auscultation.

In conditions which alter muscular function, notably left or right ventricular failure, an additional sound may appear during diastole which is commonly termed a gallop sound and the rhythm referred to as a gallop rhythm, from its resemblance to the canter of a galloping horse.[13,19,20] The phenomenon has achieved clinical significance in that it is almost invariably associated with a failing ventricle and tachycardia. Supposedly, it rarely if ever is audible at rates below 100. A gallop sound consists of usually one to seven coarse vibrations of very low frequency as compared to a murmur which consists of a series of finer, more regular and more numerous vibrations. Evans[9] has given an excellent graphic differentiation of sounds versus murmurs. He states that in the case of a sound the vibration is coarse and the distance between each vibration forms a square in relation to a millimeter scale. In the case of a murmur the vibrations are finer and form an oblong. Additional sounds may occur during systole but these are usually of no real clinical significance and therefore should not be called gallop sounds. Extra sounds during both diastole and systole may be confused with splitting or reduplication of the first or second heart sound, particularly with rapid rates.

The term triple rhythm, or three-sound rhythm, has been introduced in order to encompass conveniently all of these various extra heart sounds. Our classification, based upon the work of a number of authors, is as follows:

I. Diastolic sounds
  A. Pathologic
    1. Protodiastolic gallop rhythm
    2. Presystolic gallop rhythm
    3. Summation gallop rhythm
    4. Opening snap of mitral stenosis
  B. Physiologic
    1. Protodiastolic sound (third heart sound)
    2. Presystolic sound (auricular sound)
    3. Fusion sound (Wolferth and Margolies[22])

II. Systolic Sounds
  A. Pathologic
    1. Pulmonary early systolic sound (dilatation of the pulmonary artery, Leatham and Vogelpoel[23])

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B. Non-pathologic
   1. Systolic click, tap, knock, scratch, etc.
   2. Systolic sounds
      (*a*) Aortic systolic sound
      (*b*) Apical systolic sound
   3. Reduplication of normal heart sounds

Protodiastolic Gallop and Physiologic Third Heart Sound.[12,22,24–31] The protodiastolic gallop sound, or accentuated third heart sound, occurs early in diastole during the first phase of ventricular filling, or that of "rapid passive filling." Since the timing is identical whether the sound is pathologic or physiologic, the gallop and third heart sound will be described together.

The best description of the third heart sound is that written by William Thayer[24] in 1908. He was able to hear a third heart sound in 65 per cent, of young people with thin chest walls. He states: "This sound is softer and of lower pitch than the second sound; sometimes it is a dull, distant thud; sometimes merely a hum; it occurs shortly after the second sound, i.e., at the beginning of the long pause. It is, however, always appreciable at a time or later than that occupied by a true reduplication of the second sound, and it is audible only or with greatest intensity at or near the apex. In some cases it may be heard over the lower part of the right ventricle. At times, the sound is followed by the faintest suggestion of an echo resembling a slight early mitral diastolic murmur. . . . The quality of the sound is low pitched and clear with no suspicion of harshness or anything suggesting a murmur." He observed that the sound occurred at the beginning of the protodiastolic wave of the apex cardiogram, and simultaneous with the h wave of the jugular pulse tracing or immediately after the fall of the v wave. The sound was best heard with the patient on his back or left side during the short interval between expiration and inspiration. His cases all had relatively slow pulse rates (50–88). It was his impression that the sound was clear as compared to the dull sound of a gallop and distinguishable from the opening snap of the mitral valve with its short snapping quality. Wolferth and Margolies[22] observed no essential differences in the quality, location, time relations or influence of posture or various maneuvers to alter the sounds in distinguishing gallop from physiologic third heart sounds. They found that aside from the decreasing frequency with advancing age the only differential criterion was the status of the cardiac function. Bramwell[27] emphasizes that the physiologic third heart sound occurs without evidence of abnormality of cardiac function. He presents several differential points, namely: (1) gallop sounds are easily palpable as well as audible (except in emphysematous patients); (2) the accessory sound in gallop rhythm is only a dull thud, an abnormality of rhythm often more obvious on palpation; (3) the normal impulse produces a single thrust but the gallop impulse is a double wave with two components similar to each other, and (4) the sounds in gallop rhythm are almost evenly spaced whereas the physiologic third heart sound is obviously more closely related to the preceding second sound. The sound usually consists of one slow vibration which follows the second sound by 0.10 to 0.21 seconds (usually 0.13 to 0.18). If the second sound is split, the time relationship is maintained with one of the components. With reference to other phenomena, Luisada[12] states that it coincides with the termination of rapid relaxation in the electrokymogram of the left ventricular wall and slightly precedes the peak of the L wave of the ballistocardiogram. It has an average duration of 0.059 seconds but may vary from 0.050 to 0.061 seconds.

The physiologic third heart sound has been said to arise from vibrations of the A-V valves. It can be heard on direct auscultation of the heart in the open chest. The protodiastolic gallop supposedly results from the very rapid inflow of blood during early diastole into a dilated and flabby ventricle whose distensibility has been altered. The sound apparently arises from vibrations set up by the impact of the ventricle against the chest wall. Elevated pulmonary venous and left auricular pressure in the presence of an accelerated heart rate are factors which intensify this phase of rapid filling and predispose to the protodiastolic gallop. The sound may be heard in the presence of auricular fibrillation since its genesis does not depend upon auricular contraction.

Presystolic Gallop.[27–32] The presystolic gallop sound presumably represents an accentuated auricular sound. Its position actually depends upon the time of auricular contraction, but the sound usually occurs 0.08 to 0.14 seconds after the beginning of the P wave of the electrocardiogram. The average time of onset is 0.05

seconds after the peak of the P wave. Thus with A-V conduction defects the extra sound may precede the first sound by a considerably longer period, depending upon the P-R interval. In the case of a shortened P-R interval the split between the gallop and the first sound may be no wider than that between a reduplicated first sound. In view of these observations, Wolferth and Margolies point out that a wide split between the extra sound and the first sound favors a gallop whereas a narrow split has no differential value. Lian[21] refers to the exceptional situation in which the silent interval between the gallop sound and the first sound is lacking. He terms this a delayed presystolic gallop (galop présystolique retardé). The differentiation between this sound and a split first sound depends on whether the double sound precedes the summit of the R wave of the electrocardiogram or whether both vibrations follow the summit of the R wave, as is the case in splitting of the first heart sound. With reference to other time factors, the presystolic gallop sound occurs at the same time as a large distinct a wave of the apex cardiogram and the a wave of the jugular pulse. The auricular wave of the apex cardiogram is of large size in the case of a presystolic gallop.[31] It also coincides with point G of the ballistocardiogram and a small positive atrial wave of the electrokymogram of the left ventricle and with the descending limb of the negative atrial wave of the electrokymogram from the right or left atrial walls.[12] It is obviously not heard in the presence of auricular fibrillation. The sound is recorded best at the apex or midprecordium, especially in the left decubitus position and also in the epigastrium. It occurs during the peak of the third phase of ventricular diastole or the period of "rapid active filling" due to auricular contraction. Bond[31] presents an excellent discussion of the dynamic factors concerned with the production of this extra sound. He states, "As long as the damping action of the ventricle is preserved, auricular contractions remain inaudible. If, however, the ventricle has lost its silencing power, the reason for this change can only be an alteration in the state of its wall. (Amount of damping is proportional to the yielding capacity of normal ventricular muscle in diastole.) We must assume that the ventricular wall is no longer in a state of complete relaxation in diastole, but now offers a marked resistance to the entrance of blood during auricular systole.

"The pressure wave produced by the contracting auricle meets with a ventricular wall which no longer yields passively to every impulse; the pressure is raised suddenly in the large common cavity comprising both auricle and ventricle, and the whole of its surrounding wall is thrown into tranverse vibrations. These, transmitted to the wall of the chest, are heard as the familiar third sound of gallop rhythm. As has often been stated, it is best heard near the apex, which is that portion of the vibrating muscle mass closest to the wall of the chest. In this conception, the extra sound is a combined auricular and ventricular effect, and the participation of the ventricle explains why a sound, auricular in origin, should be so well perceived over the ventricle." Thus increased diastolic tension of the ventricle and increased intra-auricular pressure are regarded as the main factors in the causation of the extra sound.

In patients with normal rhythm or normal hearts, no distinct auricular sound is audible. In heart block, however, sounds synchronous with isolated auricular contractions may be heard. The first sound may be reinforced or accentuated in cycles where the extrasystole happens to synchronize with auricular contraction.

In 1888, Rouchès[33] introduced the term, "claquement d'ouverture de la mitrale" or opening snap of the mitral valve. He suggested that the sound was produced by the sudden stretching of a stenosed mitral valve as the blood rushed from left auricle to left ventricle. This extra sound has acquired added significance[35] with the advent of mitral valve surgery since it indicates the presence of a flexible or operable valve. It is invariably accompanied by a snapping mitral first sound. It has been observed that this sound is generally not present in the event of gross calcification of the valve, slight stenosis or marked insufficiency. Mounsey[34] made a clinical and phonocardiographic study of thirty-three patients with mitral stenosis as their predominant valvular lesion. The opening snap was heard in twenty-eight cases, in four it was seen only on phonocardiography, and in one the sound could not be elicited. The sound is composed chiefly of high frequency vibrations of brief duration (0.005 to 0.01 seconds). It was best heard over the supramammary area although in most cases it was heard equally well along the left sternal border and over the mitral area, least often over the pulmonic area. The average interval between the beginning of the

second sound and the opening snap was 0.07 seconds with a range of 0.03 to 0.14 seconds. He found that this distance varied directly as the length of the diastolic interval. In twenty-seven of the thirty-two cases the mitral snap was followed closely by a mid-diastolic murmur. In thirty-one of the thirty-three patients both splitting of the second sound and an opening snap were present. In every instance the split sound was heard loudest in the pulmonic area. The third sound is of much lower frequency than the opening snap. A helpful differential point in patients with physiologic splitting was the widening or disappearance of the split with deep inspiration. Such variation does not occur with splitting in bundle branch block. The opening snap coincides with the beginning of the descent of the v wave of the jugular pulse.

Summation Gallop.[22] In the event that the time zones of both protodiastolic and presystolic gallop sounds merge, an augmented or summation sound may be produced. This situation occurs in cases of tachycardia, A-V block, sinus arrhythmia or auricular extrasystoles. The sound may occur in failure but also in normal persons with tachycardia or in patients with rheumatic fever who exhibit tachycardia and prolonged P-R intervals. Wolferth and Margolies[22] in their series observed that the critical rate (rate at which the two extra sounds merge) was usually between 100 to 130 beats per minute. If the P-R interval was prolonged, however, the critical rate tended to be lower (90–100).

Systolic Sounds.[23,36–42] Leatham and Vogelpoel[23] recently described perhaps the only systolic sound considered pathognomonic of heart disease; namely, a pulmonary early systolic sound in patients with dilatation of the pulmonary artery. This sound was originally described by Lian and co-workers in 1937 and 1942 as an early systolic sound (claquement protosystolique) heard over the pulmonary area in patients with pulmonary stenosis and with dilatation of the pulmonary artery, and also at the aortic area in patients with aortic valve disease. Leatham and Vogelpoel performed detailed studies of this sound combined with catheterization of the pulmonary artery. The sound was found to be high-pitched and often sharp like a click. It was loudest over the pulmonic area and during expiration, at times almost disappearing during inspiration. It is not affected by position and has a constant place in the cardiac cycle. The sound gives the impression of wide splitting of the first heart sound but has more of a click-like quality. The time interval between the onset of major high frequency components of the first sound and the onset of the pulmonic extra sound averages 0.07 seconds with a range of 0.05 to 0.14 seconds. Of fifty patients demonstrating this sign on auscultation forty-four had pulmonary hypertension which was confirmed by cardiac catheterization in forty-two. Sixteen of the patients had mitral stenosis, seven had a patent ductus arteriosus, ten had a ventricular septal defect, seven had an atrial septal defect, three had primary pulmonary hypertension, and one had transposition of the great vessels. In the seventeen cases with patent ductus and ventricular septal defect the pulmonary pressure was apparently high enough to reverse the usual left-to-right shunt and thus abolish or diminish the continuous or long systolic murmurs, respectively. The authors state that the presence of this sound in patients with mitral stenosis indicates a severe degree of pulmonary hypertension, but that its absence does not mean lower pressures.

The so-called systolic gallop was first described by Cuffer and Barbillon[13] in 1887 as "mesosystolic gallop." They observed the sound in four patients with typhoid fever and in two with tuberculosis. Potain[13] stated that the sound could be heard best over the aortic area and regarded it as an arterial phenomenon subsequent to diminished elasticity and tonicity of the aorta. Wolferth and Margolies[36] were able to make the diagnosis of systolic gallop eight times in ten years despite the fact that they were particularly interested in the study of extra heart sounds. Thompson and Levine[37] observed thirty-five cases over an eleven-year period and during the same interval observed 186 patients with diastolic gallop rhythm. Their incidence of systolic gallop was therefore 16 per cent. They found that the extra sound resembled the first heart sound although the intensity was variable. The sound was heard only at the apex or with maximum intensity there in most patients. The patient's position also considerably influenced the intensity of the vibrations. The heart rate in most cases ranged from 70 to 80 beats per minute. These authors emphasize the benign nature of the sign which for the most part was found in "nervous people," two-thirds of whom had no evidence of heart disease. During the period in which their patients were observed 46 per cent of those with diastolic gal-

lop rhythm died or were presumed to have died whereas none of the patients with systolic gallop expired. After reviewing the many theories of genesis in the older literature, they summarized that, "Opinion as to mechanism is then roughly divided into two basic ideas, that of a lengthened period of isometric contraction of the ventricle with resultant dissociation of the elements of the normal first sound and that of production by a diseased or weakened aortic wall." White[43] mentions that the cause is unknown but may possibly be due to deformity of valves, chordae tendinae, pericardium or pleura. Wolferth and Margolies[36] suggest that the sound may arise from the pressure of the contracting heart against some emphysematous area in the overlying lung. They recognize two types of systolic gallop rhythm exclusive of the sounds which may fall between the first and second heart sound; namely, aortic and apical systolic gallop rhythm. They further state that the mid-systolic click bears no resemblance to the systolic gallop except that it falls between the first and second sound. It may have three or more components and is usually heard best near the apex.

The mid-systolic click is so described because of its obvious clicking quality. The quality of the sound has been variously described as rough, superficial, dry, vibrant, grating, tapping, etc. It is highly susceptible to positional and respiratory variations. The extracardiac origin of the sound has been very clearly demonstrated by Becker and Halpern[41] who found that the sound was not constantly related to any part of the cardiac cycle as determined by simultaneous jugular, carotid pulse and electrocardiographic tracings. In their case the sound varied from mid-systole to protodiastole in time. It is a completely benign but often striking sound and must occasionally be differentiated from a diastolic gallop or mitral opening snap.

Our observations with respect to gallop rhythm parallel those of Bramwell.[27] They are predicated upon the thesis that if the accepted physiologic explanations for true gallop rhythm are valid, then, with few exceptions, the demonstration of such a sound should be synonomous with the demonstration of heart failure. Debate as to the advisability of applying the term gallop rhythm to those cases with diastolic sounds which are inaudible and can be elicited only by graphic registration would seem to misinterpret the clinical connotation of this important sign. The application of such terms as triple rhythm to the over-all group of extra sounds is helpful.

One of the authors (W. B. P.) has found a simple bedside technic to be extremely helpful in the differentiation of gallop rhythm from other types of triple rhythm in approximately three-fourths of the patients who exhibit this sign. It has been observed that consequent to the slowing of ventricular rate effected by carotid sinus pressure, a true gallop sound will invariably become inaudible or disappear. The observation that variations in rate have a pronounced effect on gallop rhythm is not new; however, to our knowledge the utilization of a clinical test based on this fact for the simple and accurate differentiation of true gallop rhythm from other types of triple rhythm has not been generally practiced.

We have found the right carotid sinus to be almost invariably more effective than the left in producing slowing of the ventricular rate.

Ferris et al.[44] found no particular predominance of either sinus in reproducing the symptoms of the "cerebral" type of carotid sinus syncope, nor did Weiss and Baker.[45] Our observations would suggest that the right carotid sinus pressure is more effective in slowing the ventricular rate in patients with gallop rhythm.

MATERIAL AND METHODS

Simultaneous electrocardiograms and phonocardiograms were obtained from a series of thirteen consecutive patients who demonstrated a distinct gallop rhythm. In order to test the validity of the procedure, similar studies were carried out in four patients with complete bundle branch block, one patient with physiologic splitting, and five patients with extra sounds during systole. In three patients, right, left and bilateral carotid sinus pressure failed to produce a significant slowing of the ventricular rate. One of the three (L. M.) did, however, develop a slow rate with disappearance of his gallop rhythm following bilateral compression of his eyeballs (oculocardiac reflex). A tabulation of these cases is presented in Tables I and II.

CASE REPORTS

Figure 1 is the phonocardiogram of J. L. (Table I), a sixty-eight year old Negro man, who entered the hospital because of moderate hypertension complicated by early left ventricular failure. Auscultation revealed a diastolic

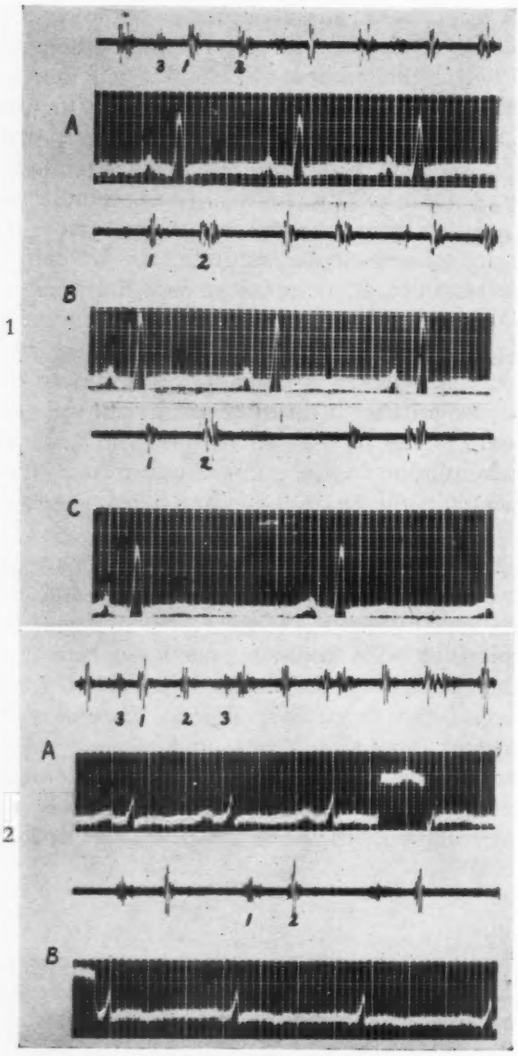

FIG. 1. Apical phonocardiogram from J. L. reveals a mid-diastolic gallop in A, which consists of one coarse vibration merging with three finer vibrations. Following right carotid sinus pressure (between A and B) the heart rate slowed from 105 to 60 beats per minute in C. In B, between the third first heart sound and the preceding second heart sound, the single coarse vibration has separated from the three finer vibrations, indicating the presence of a summation gallop in A. This separation occurs at a rate of 83. The finer vibrations follow the peak of the third P wave in B by an interval of 0.04 seconds and the single coarse vibration follows the preceding second sound by an interval of 0.11 seconds. The gallop sound became inaudible when the rate slowed below approximately 92 beats per minute.

FIG. 2. Phonocardiogram from E. F. reveals a presystolic gallop sound in A. The ventricular rate is 118. Following right carotid sinus pressure, the heart rate slowed to 75. The gallop sound is no longer visible in B with the rate slowed to 90 and became inaudible with a rate of approximately 95.

gallop rhythm. Electrocardiogram was interpreted as sinus tachycardia and left ventricular strain. Phonocardiogram from the apical region revealed one coarse diphasic vibration merging with three finer vibrations (Fig. 1, A). The ventricular rate at this point was 105. Following pressure on the right carotid sinus, the ventricular rate slowed to 60. With a rate of 83 the single coarse vibration separated from the three finer vibrations so that in B, Figure 1, the finer vibrations can be seen to follow the peak of the third P wave by an interval of 0.04 seconds and the single coarse vibration to follow the preceding second sound by an interval of 0.11 seconds. These sounds were inaudible when the rate slowed below approximately 92 beats per minute.

Figure 2 is the phonocardiogram of E. F. (Table 1), a forty-year old Negro man, who entered the hospital because of anasarca and congestive heart failure. He was a known alcoholic. Auscultation of the heart revealed a diastolic gallop rhythm. Despite the presence of marked cardiac decompensation, his arm-to-tongue circulation time using decholin was but ten seconds. He responded dramatically to thiamine. His electrocardiogram was interpreted as sinus tachycardia, low voltage and diffuse T wave abnormality consistent with diffuse myocardial disease. In A, Figure 2, are seen three medium coarse vibrations, presystolic in time. The ventricular rate is 118. Following right carotid sinus pressure, B, the gallop sound became inaudible and was no longer visible in the phonocardiogram. The sound became inaudible at a rate of approximately 95.

Figure 3 is the phonocardiogram of E. B. (see Table 1), a thirty-eight year old Negro man, who entered the hospital because of congestive heart failure. Auscultation revealed a diastolic gallop rhythm, which disappeared with ventricular slowing incident to pressure on the right carotid sinus. Electrocardiograms were interpreted as showing slightly prolonged intraventricular conduction and left ventricular strain. Because of failure to demonstrate an etiology for his generalized cardiomegaly he was diagnosed as having idiopathic cardiac hypertrophy. Phonocardiogram revealed a presystolic gallop sound consisting of two coarse vibrations separated by one finer vibration, A. The initial heart rate was 120. Following carotid sinus pressure, B, these vibrations disappeared from

TABLE I

GALLOP RHYTHM

Case No.	Patient	Age	Cardiac Diagnosis	Initial Heart Rate	Heart Rate When Gallop Inaudible	Type Gallop	Heart Failure Present
1	E. B.	38	Idiopathic hypertrophy	120	90	Presystolic	Yes
2	A. C.	27	Cor pulmonale	130	85	Summation	Yes
3	E. F.	40	Beri-beri	118	94	Presystolic	Yes
4	W. L.	66	Coronary	120	..	Mid-diastolic	Yes
5	J. L.	68	Hypertensive	105	92	Summation	Yes
6	L. M.	35	Hypertensive	120	98	Presystolic	Yes
7	C. M.	49	Coronary	125	..	Mid-diastolic	Yes
8	C. W.	31	Idiopathic hypertrophy	95	90	Presystolic	Yes
9	T. F.	27	Hypertensive	110	98	Presystolic	Yes
10	L. H.	44	Cor pulmonale	105	90	Presystolic	Yes
11	C. C.	26	Hypertensive	115	95	Presystolic	Yes
12	F. O.	41	Hypertensive (LBBB)	98	85	Presystolic	Yes
13	J. T.	59	Hypertensive (RBBB)	110	85	Presystolic	Yes

TABLE II

Case No.	Patient	Age	Diagnosis	Initial Rate	Maximum Slowing	Type	QRS Interval (sec.)	Variation in Position of Sound	Heart Failure Present
				A. Bundle Branch Block					
1	E. B.	61	Lung carcinoma	70	60	RBBB	0.13		No
2	F. O	41	Hypertension	98	80	LBBB	0.13		Yes
3	W. P.	60	Scleroderma	65	50	LBBB	0.14		Yes
4	J. P.	38	Rheumatic fever	87	67	RBBB	0.15		No
5	J. T.	59	Hypertension	110	85	RBBB	0.16		Yes
6	T. P.	30	Idiopathic hypertrophy	...	..	Physiologic splitting	0.08		Yes
				B. Systolic Sounds					
1	J. H.	44	Pleura carcinoma	102	70	Click		Yes	No
2	H. G.	56	Psychoneurosis	90	65	Click		Yes	No
3	E. B.	58	Emphysema	100	80	Click		Yes	No
4	S. T.	58	Cirrhosis	88	60	Apical "gallop"		No	No
5	A. S.	65	Cerebrovascular hemorrhage	65	40	Apical "gallop"		No	No

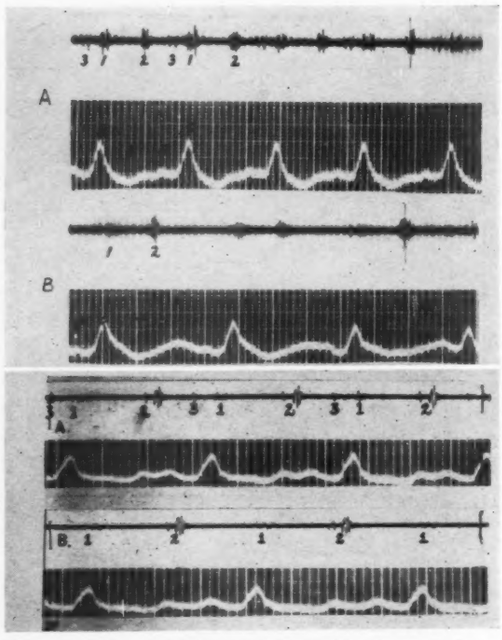

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FIG. 3. Phonocardiogram from E. B. reveals a presystolic gallop sound in A with an initial heart rate of 120. Following right carotid sinus pressure in B, these vibrations disappeared from the sound tracing. The gallop sound became inaudible at a rate of approximately 90.

FIG. 4. An apex phonocardiogram from F. O. reveals a reduplication of the second sound with the two components separated by an interval of 0.05 seconds. The simultaneous electrocardiogram reveals a complete bundle branch block (left). A presystolic sound consisting of three coarse vibrations follows the peak of the P wave by 0.06 seconds. The initial heart rate, A, is 98. Following right carotid sinus pressure, B, the ventricular rate has slowed to 84 and the presystolic gallop sound is neither audible, nor visible on the sound tracing.

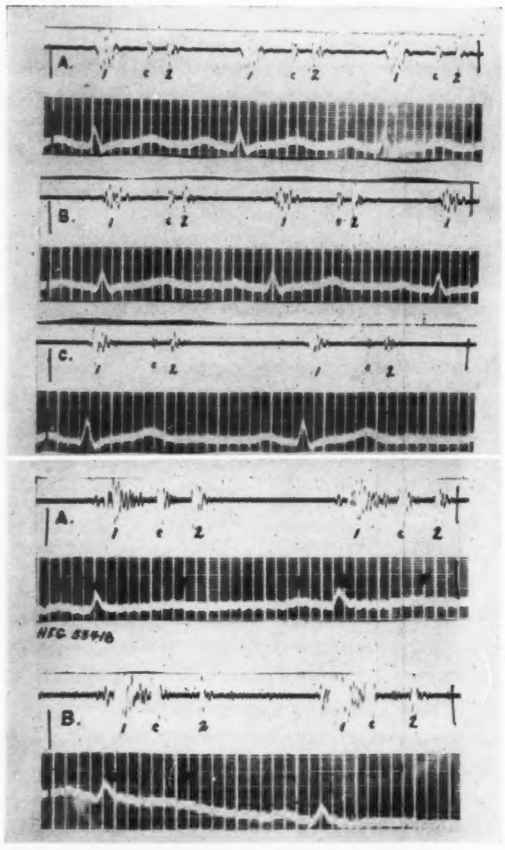

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FIG. 5. Phonocardiogram from J. H. reveals a slight systolic murmur and a mid-systolic click (*c*). The ventricular rate in A is 101. Following carotid sinus pressure the ventricular rate has slowed to 90 in B and to 73 in C. It can be observed that the click approaches closer to the second sound in B and diminishes in intensity in C.

FIG. 6. Phonocardiogram recorded from H. G. reveals a split first sound. The second component of the split first sound is obscured by a moderate systolic murmur, which extends into mid-systole where a loud systolic click is evident. In A the rate is 70 and the click occupies a position in mid-systole. In B the rate is 85 and the click has shifted toward the first sound blending with the systolic murmur.

the sound record. The extra sound became inaudible at a rate of approximately 90.

One patient (L. M., Table I) failed to slow his ventricular response following bilateral carotid sinus pressure; however, his rate slowed quickly from 120 to 85 following bilateral eyeball (oculocardiac reflex) pressure. Another patient, C. W., responded with only a very slight decrease in ventricular response (8 beats per minute). His extra sound became inaudible with a decline in rate from 95 to 90. Although inaudible on auscultation, a faint presystolic sound was still apparent in the sound tracing after this slowing. Two patients with coronary heart disease and intractable failure demonstrated loud mid-diastolic gallop sounds but failed to alter their rapid ventricular rates either with bilateral carotid sinus pressure or bilateral eyeball pressure.

Two patients with complete bundle branch block had, in addition to a presystolic gallop, wide splitting of the second heart sound. The gallop sound disappeared following carotid sinus pressure without apparent change in the reduplication of the second sound. Figure 4 is the sound tracing from one of these patients, F. O. (Tables I and II), who represents one of the cases already described. The sound tracing revealed a presystolic gallop sound consisting of

three coarse vibrations, followed by a very faint prolonged first sound, and a reduplicated second sound. The rate slowed to 80 following carotid sinus pressure. The extra sound became inaudible with a rate of 84. With slowing, the reduplication was more evident with only a very slight change in the interval between the split sounds. Figures 5 and 6, J. H. and H. G., represent two examples of the so-called systolic click. H. G. has in addition a systolic murmur. This sound is easily differentiated by its characteristic "clicking" quality and the marked variation in the position which it occupies in the cardiac cycle with changes in rate, position and respiration.

COMMENTS

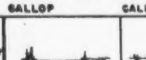
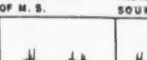
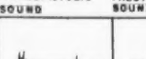
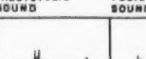
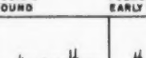
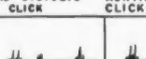
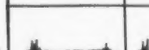
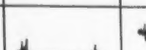
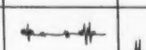
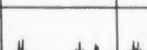
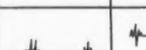
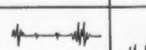
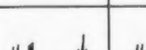
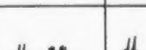
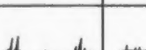
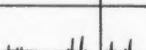
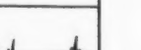
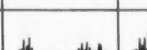
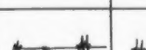
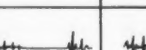
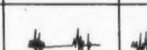
The use of carotid sinus pressure and the subsequent slowing of ventricular rate has been effective in rendering the gallop sound inaudible in eleven of thirteen patients, or 85 per cent of the cases reported upon. It has also been a valuable adjunct in the differential diagnosis of other types of triple rhythms. In keeping with the observations of King,[38,39] the authors have observed that the phenomenon which bears his name, viz., the reduplicated sounds which result from asynchronous contraction of the ventricles (and therefore asynchronous closure of the semilunar valves) in bundle branch block are invariably feeble or distant. Exceptions to this observation have been demonstrated only in young or very thin-chested individuals and in those with a gallop sound also present. We have further observed that bundle branch block is usually associated with a slow ventricular rate. Often the asynchronism of the apex thrust may be more obvious than the sound. In contrast, the gallop sound is usually quite loud and forms a characteristic rhythm or canter in which the three sounds are rather evenly separated. Like bundle branch block, it has been stated that the gallop rhythm is often more apparent on palpation than on auscultation. The heart rate with the true gallop rhythm is invariably rapid and the sound is low pitched and dull compared with the sounds produced by reduplication which obviously resemble the valvular sounds. Systolic sounds may be heard with a slow or rapid rate and must therefore be differentiated from a diastolic gallop or reduplication. It is at times difficult to differentiate the so-called "systolic gallop" from a short mid-systolic murmur. This sound is rarely heard in patients with heart disease, and when the combination does occur represents only an incidental finding.

Although the gallop sound was present at rates above 100 in all but two patients, C. W. and F. O., the "critical rate," or rate at which the gallop became inaudible by auscultation, varied between 85 and 98. The average critical rate for the eleven patients who responded to carotid sinus pressure was 91. The heart rate in the thirteen patients with gallop rhythm varied from 95 to 130 with an average rate of 113. It was observed that the extra sound vibrations were still visible on the phonocardiogram after the sound had become inaudible. In most cases the extra sound vibrations did not disappear from the phonocardiogram until the ventricular rate had slowed approximately 5 to 10 beats below the rate where the sound first became inaudible.

Clinical observations pertinent to the differential diagnosis of triple rhythms are tabulated in Table III. It can be seen that the true diastolic gallop sounds are invariably associated with a rapid ventricular rate and are usually of moderate intensity as compared to most other accessory sounds. The intensity is subject to slight respiratory variation. Although their timing is usually obvious on the phonocardiogram, on auscultation they appear to be more evenly spaced, certainly with respect to other three-sound rhythms. The apical impulse is frequently double and the rhythm is thus sometimes more apparent to palpation. The sounds are of very low frequency and usually consist of one to three vibrations, rarely as many as seven.

The opening snap of the mitral valve is usually loud and of higher frequency than a true gallop although not so high as a click. It is heard best in the supramammary area; however, it is generally audible with equal intensity along the left sternal border or over the mitral area, more rarely over the pulmonary area. An increase in the diastolic interval with slowing of the heart rate is accompanied by a longer interval between the beginning of the second sound and the opening snap. The snap usually follows a split second sound, which sometimes makes differentiation difficult. The split second sound, however, is invariably loudest over the pulmonary area. Inspiration tends to lengthen the interval between the split sound whereas expiration shortens it. In contrast, the sound of the opening snap may vary its intensity with respiration but not its timing. A physiologic

TABLE III

	PROTODIASTOLIC GALLOP	PRESYSTOLIC GALLOP	SUMMATION GALLOP	OPENING SNAP OF M. S.	PROTODIASTOLIC SOUND	PRESYSTOLIC SOUND	FUSION SOUND	PULMONARY EARLY SYSTOLIC CLICK	MID-SYSTOLIC CLICK	AORTIC SYSTOLIC CLICK	BBB WITH REDUPLICATION	PHYSIOLOGICAL SPLITTING
TYPE OF ACCESSORY SOUND.												
EFFECT OF CAROTID SLOWING												
EFFECT OF INSPIRATION												
EFFECT OF EXPIRATION												
EFFECT OF POSTURE	UNCHANGED	UNCHANGED	UNCHANGED	UNCHANGED	LEFT RECUMBENT POSITION..	SLIGHT	SLIGHT	0	MARKED VARIATION	SLIGHT	0	SLIGHT
RATE	100+	100+	100+	VARIABLE	SLOW	SLOW	RAPID	VARIES	VARIES	SLOW	SLOW	VARIES
FREQUENCY	LOW	LOW	LOW	HIGH	LOW	LOW	LOW	HIGH	HIGH	LOW	MEDIUM	MEDIUM
INTENSITY	+++	+++	++++	+++	+	+	+	+++	++	++++	+	++
QUALITY	DULL	DULL	DULL	SHARP SNAPPING	DULL	DULL	DULL	CLICKING	CLICKING	CLICK-LIKE	VALVULAR	VALVULAR
PALPABILITY	+++	+++	++++	0	0	0	0	0	0	0	+++	0
AREA BEST HEARD	APEX	APEX	APEX	SUPRAMAMMARY	APEX	APEX	APEX	PULMONARY	APEX	AORTIC	BASE	APEX
IMPORTANT ASSOCIATED CONDITIONS	C.H.F.	C. H. F.	C H F	M. S.	NONE	A-V BLOCK	A-V BLOCK	PULMONARY HYPERTENSION	NONE	NONE	B. B. B.	NONE

third heart sound is extremely rare in association with pure mitral stenosis.

Presystolic and fusion sounds occur in individuals with A-V conduction disturbances. In the presence of certain arrhythmias the presystolic sound may be accompanied by variations in the intensity of the normal first sound.

The pulmonary early systolic sound is loud, high pitched, and often has a sharp, clicking quality. It may give the impression of wide splitting of the first sound. Expiration accentuates the pulmonary systolic sound.

The so-called mid-systolic click has a characteristic quality and is prone to wander throughout systole and even into early diastole with changes in rate, respiration and posture.

The reduplicated sounds in bundle branch block are invariably distant and often more obvious on palpation. In the absence of heart failure, the rate is invariably slow. Audible splitting of the second sound rather than the first is the usual finding on auscultation.

SUMMARY

Carotid sinus pressure with consequent slowing of the heart rate caused the accessory sound in gallop rhythm to become first inaudible and then to disappear from the sound tracing in 85 per cent of thirteen cases reported by the authors. The validity of the technic as a method of differential diagnosis of triple rhythms has been affirmed through observations on numerous patients with various types of triple rhythm, eleven of whom are discussed. Whereas the true gallop sound invariably became inaudible when the ventricular rate slowed below an average "critical rate" of 91, other types of extra sounds became more obvious because of changes in timing, intensity or clarity. A classification of three-sound rhythms has been presented with a detailed acoustic, physiologic and clinical discussion of each. The pertinent clinical aspects of the differential diagnosis of triple rhythm have been summarized in tabular form.

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Pulmonary Stenosis and Interatrial Communication with Cyanosis*

Hemodynamic and Clinical Study of Ten Patients

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In patients who have pulmonary stenosis and atrial septal defect, blood may be shunted through the defect in either direction.[1-3] When the existing shunt is large and completely or predominantly right to left, the condition clinically may resemble the tetralogy of Fallot.[1,4-7]

It is the purpose of this paper to present clinical and hemodynamic data concerning a series of ten patients who had pulmonary stenosis and interatrial communication and were moderately or severely cyanotic. In all the patients the clinical findings indicated clearly the presence of pulmonary stenosis with an associated right-to-left shunt. It may not be possible to be certain of the location of the right-to-left shunt and in several of our patients a diagnosis of tetralogy of Fallot was considered most likely before cardiac catheterization.

In this paper the term "interatrial communication"[8] will be used to include a true defect located in any portion of the atrial septum, and also the condition of valve-competent patent foramen ovale which occurs in 25 per cent of normal persons. Under normal dynamic conditions the pressure in the left atrium exceeds that in the right atrium during a considerable portion if not all of the cardiac cycle and this difference is considered the basis for the left-to-right direction of the interatrial shunt in the usual uncomplicated case of atrial septal defect. In an individual with a valve-competent patent foramen ovale, this normal pressure gradient tends to close the potential interatrial communication and no left-to-right shunt occurs. When the pressure in the right atrium exceeds that in the left atrium, the shunt in atrial septal defect becomes partially or completely right to left. If for any reason the right atrial pressure is greater than that in the left atrium in a person who has valve-competent patent foramen ovale, the pressure gradient will tend to open this potential interatrial communication and cause a right-to-left shunt. Accurate localization of the site of the right-to-left shunt has been greatly facilitated by the introduction of indicator dilution technics. It is still, however, difficult or impossible to distinguish between valve-competent patent foramen ovale and valve-incompetent foramen ovale (atrial septal defect) by cardiac catheterization in cases in which the shunt is completely from right to left.

CASE REPORTS

The majority of the patients seen at the Mayo Clinic who have tetralogy of Fallot and in whom the pulmonary artery shadow is less prominent than normal have not been referred for cardiac catheterization up to the present time. This form of investigation is reserved for those in whom the clinical features are unusual or suggest another lesion. Some of the cases to be described were referred to the clinic with the diagnosis of tetralogy of Fallot.

The major clinical data in the present series of ten patients are summarized in Table I. Roentgenograms of Cases I, III and X are reproduced in Figure 1 and electrocardiograms of these patients are reproduced in Figure 2.

CASE I. The patient, aged twenty-one years, registered at the Mayo Clinic in February, 1954. He complained of severe effort dyspnea and fatigue, which had become progressively greater

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since 1952. He had been told by his parents that he was cyanotic at birth. His local physician referred him to the clinic for evaluation and possible cardiac surgery.

CASE II. The patient, aged nineteen years, registered at the clinic in August, 1952. She stated that cyanosis had been noted at two weeks of age associated with pneumonia. There had been no recurrence of cyanosis until the age of seven years. Since that time it had been persistent and associated with easy fatigability. There had been two recent transient episodes of paroxysmal tachycardia.

CASE III. The patient, aged five years, was registered at the clinic in February, 1954. The main complaints were shortness of breath, fatigue and palpitation on mild exertion. A cardiac murmur and cyanosis had been noted at birth, and cyanosis had been present since birth, exaggerated with crying and exertion. The patient sat down when tired but did not squat.

A chest roentgenogram disclosed slight enlargement of the cardiac silhouette and suggestive evidence of a right aortic arch. This was verified by fluoroscopy.

TABLE I

CLINICAL DATA IN TEN CASES OF PULMONARY STENOSIS AND INTERATRIAL COMMUNICATION

		Case									
		I	II	III	IV	V	VI	VII	VIII	IX	X
Age (yr.)		21	19	5	13	5	22	3	18	23	23
Symptoms	Grade of cyanosis	3	1	2	1–2	2–3	3	2	2–3	2–3	1
	Cyanosis first noted	Birth	2 wk.; 7 yr.	Birth	Birth	Birth	Infancy	Infancy	Birth	Birth?	Childhood?
	Grade of clubbing	3	None	2	None	2	3	1	2	2	1–2
	Effort dyspnea and fatigue	Marked	Moderate?	Moderate	Present	Marked	Mild	Marked	Severe	Marked	Moderate
Auscultatory signs	Systolic murmur II–III space	Grade 2, coarse	Grade 3, rough	Grade 3	Grade 3	Grade 2	Grade 2, coarse	Grade 2–3, coarse	Grade 3, rough	Grade 3	Grade 3, rough
	Second sound	Not identified	Not identified	Single	Single	Single	Not identified	Single	Single	Not identified	Not identified
Radiologic appearance	Heart enlargement	R.V.+	Normal	Slight	Slight	R.V.+	Moderate	R.V.+	Normal	Slight	Slight
	Pulmonary artery shadow	Visualized+	Visualized+	Not visualized 0	Visualized+	Prominent ++	Not visualized 0	Prominent +++	Prominent ++	Prominent +++	Prominent ++++
	Vascular mark	Normal	Normal	Decreased	Normal	Normal	Slightly decreased	Decreased	Decreased	Normal	Normal

CASE IV. The patient, aged thirteen years, registered on this admission in August, 1953, but had had prior examinations at the clinic in 1949 and 1950. A tentative diagnosis of pulmonary stenosis with ventricular septal defect had been made on the earlier admissions. The patient had been cyanotic at birth and had had persistent cyanosis since then, especially with effort. There were associated fatigability and effort dyspnea.

CASE V. The patient, aged five years, was registered at the clinic in October, 1952. He complained of marked effort dyspnea and fatigue. His mother stated that a few days after

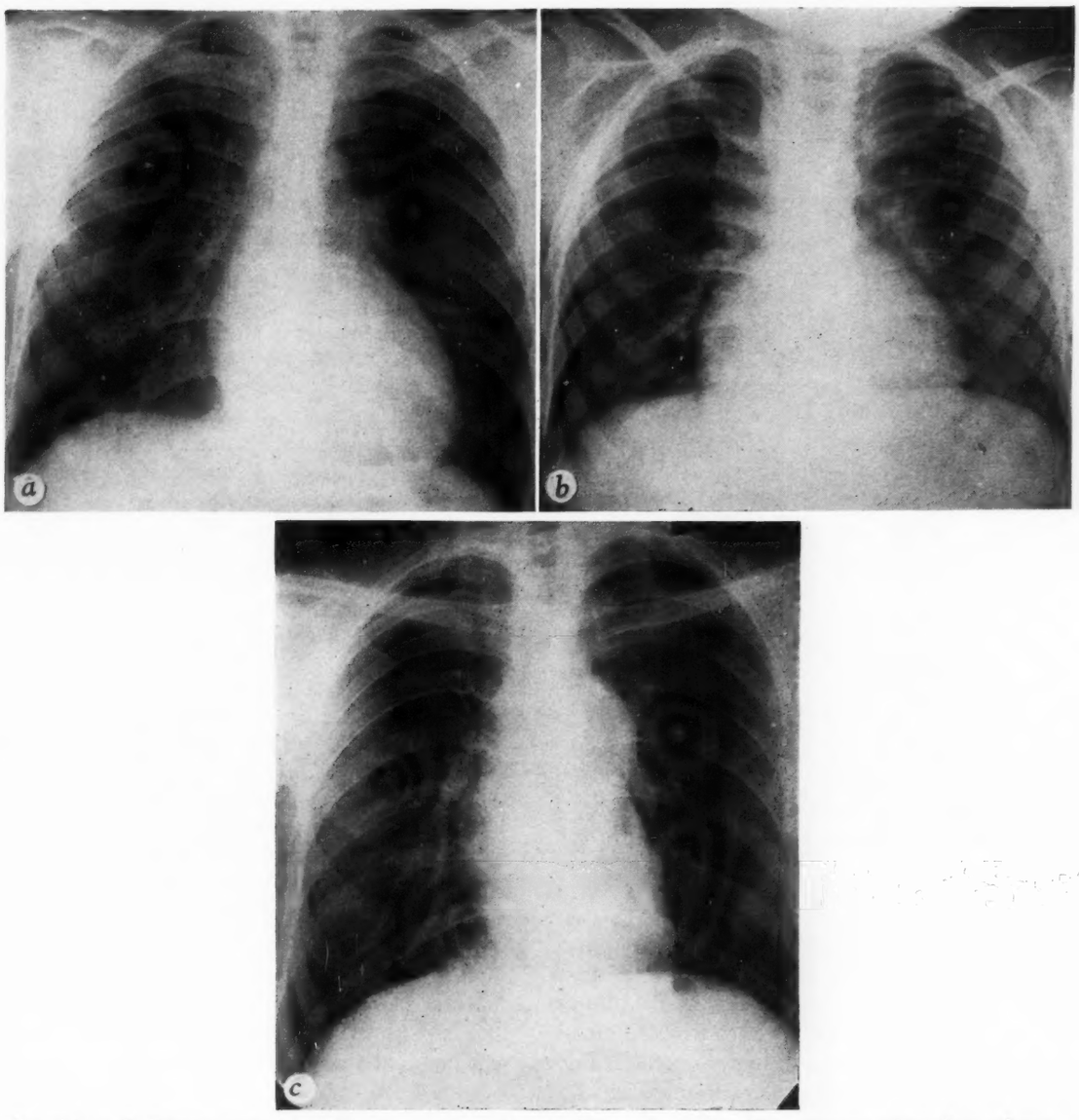

FIG. 1A to C. Postero-anterior roentgenograms of chest in Cases I, III and X. The presence of cardiac enlargement, the prominence of the pulmonary artery and the appearance of pulmonary vascular markings are given in Table I.

birth he had had an episode of unconsciousness and cyanosis when crying. During the second week of life he had two similar episodes. After this there were no further episodes of unconsciousness but cyanosis on crying and exertion was noted. A heart murmur was noted first at fifteen months of age by a pediatrician.

CASE VI. The patient, aged twenty-two years, registered at the clinic in July, 1952. He complained of mild effort fatigue and dyspnea. He had been told that cyanosis had been present since infancy and that he squatted in childhood when fatigued. He stated further that in childhood he could walk only twenty yards at one time, but that his exercise tolerance had improved with time and that he was now able to go up four flights of stairs without rest.

On examination the systemic blood pressure varied from 150 to 220 mm. of mercury systolic and from 115 to 170 diastolic. This was the only patient in the present series who had an elevated systemic arterial pressure. Urinalysis disclosed a specific gravity of 1.010, grade 2 albuminuria, grade 2 erythruria and hyaline and granular

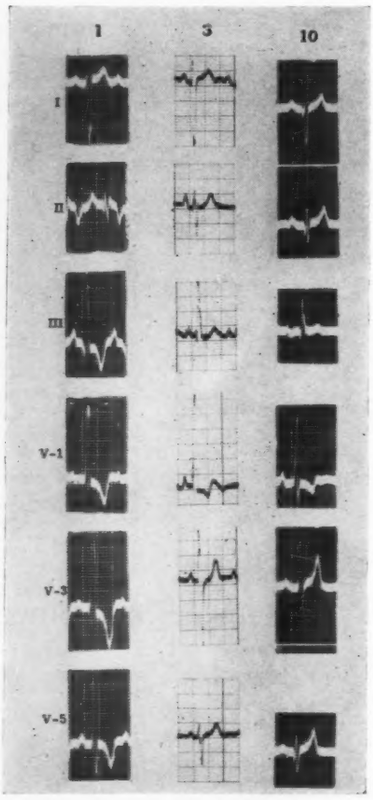

FIG. 2. Electrocardiograms for Cases I, III and X. The tracing for Case I was recorded at half the standard voltage. Note the moderate to severe right ventricular hypertrophy.

casts. The blood urea was 36 and 28 mg. per 100 cc. on two occasions. This patient died following operation. Sections of the kidneys revealed the presence of chronic glomerulonephritis with secondary hypertension. The improvement in exercise tolerance which the patient noted might be related to the development of systemic hypertension but the time of onset of the hypertension is not documented. There was moderate thoracic scoliosis.

CASE VII. The patient, aged three years, was registered at the clinic on this admission in April, 1952. A heart murmur had been noted at birth, and cyanosis on crying had been present in infancy. There had been progressive effort fatigue and dyspnea in the six months before the present examination. Squatting with fatigue was also present.

CASE VIII. The patient, aged eighteen years, registered at the clinic in November, 1950. She complained of effort dyspnea, fatigue and palpitation, which had been particularly severe since 1945. Cyanosis had been present at birth and clubbing had been noted in infancy.

CASE IX. The patient, a twenty-three year old man, registered at the clinic in April, 1953, desiring evaluation of his cardiac status. He was unable to obtain employment as a television repair man because of his cyanotic appearance and effort dyspnea. He had probably been cyanotic at or soon after birth but had not been significantly disabled until the age of seventeen years.

CASE X. The patient, aged twenty-three years, registered at the clinic in April, 1953. He planned on marriage in the near future and wished evaluation of his cardiac status. He was particularly interested in the possibility of cardiac surgery. He had noted easy fatigue, decreased exercise tolerance and cyanosis with moderate to severe exertion for as long as he could remember.

METHODS

The patients were studied by the cardiac catheterization technic, employing the method of Cournand and Ranges[9] as modified in apparatus and technic by Wood and associates.[10–12] Intracardiac and systemic arterial pressures were recorded using strain-gauge manometers.[13] The oxygen content of systemic arterial blood was determined by the method of Van Slyke and Neill,[14] and oxygen capacity was obtained manometrically after equilibration by the method of Sendroy[15] as modified by Roughton and associates.[16] For the recognition and localization of left-to-right intracardiac shunts, if present, multiple small samples of blood were obtained in the various chambers of the heart in rapid succession and the saturation of such samples was determined as they were drawn through a cuvette oximeter[17] attached via a three-way stopcock to the distal end of the cardiac catheter. Use of this instrument greatly facilitated the establishment of a certain diagnosis in many instances.

For the calculation of pulmonary and systemic blood flow Fick's principle[18] was used:

$$\dot{Q}_p = \frac{\dot{V}_{O_2}}{(C_{pv_{O_2}} - C_{pa_{O_2}})}; \dot{Q}_s = \frac{\dot{V}_{O_2}}{(C_{sa_{O_2}} - C_{pa_{O_2}})}$$

Where $\dot{Q}_p$ = pulmonary flow, $\dot{Q}_s$ = systemic flow, $\dot{V}_{O_2}$ = oxygen uptake (L./min.), $C_{pv_{O_2}}$ = oxygen content (cc./L.) of pulmonary vein

blood,* $C_{pa_{O_2}}$ = oxygen content (cc./L.) of pulmonary artery blood, $C_{sa_{O_2}}$ = oxygen content (cc./L.) of systemic (radial) artery blood.

The right-to-left shunt (assuming no left-to-right shunt) was calculated from the relationship

$$\text{R-L shunt per cent} = \frac{\dot{Q}_s - \dot{Q}_p}{\dot{Q}_s} \times 100$$

expressed as a percentage of systemic flow.

In two patients satisfactory values for oxygen consumption were not obtained; in these the proportion of shunt was calculated on the basis of the oxygen saturation values according to the method of Burchell and Wood.[19]

Indicator dilution curves were recorded photographically, usually while the patient breathed 100 per cent oxygen, but at times while he breathed air, using cuvette and earpiece oximeters. Injections of T-1824 in doses appropriate to the size of the patient were made into the chambers of the heart and great vessels at different times during the catheterization procedure.[20]

HEMODYNAMIC FINDINGS

All of the patients (Table II) were found to have elevated right ventricular pressures. In six patients the right ventricular systolic pressure was greater than the radial artery pressure. In two patients these pressures were equal. In one patient the radial artery systolic pressure was greater than the right ventricular systolic pressure and in one patient, a child, systemic arterial pressure was not recorded.

The blood oxygen capacity was elevated in each patient. In four patients the values obtained were 30 volumes per 100 cc. or slightly higher.

Blood flow, expressed in liters per minute, was calculated in the pulmonary and systemic circulation in six patients. The pulmonary flow in each case was found to be less than the systemic flow. The right-to-left shunt was large in each patient. In five patients it was 50 per cent or more of systemic flow.

The diagnosis of pulmonary stenosis was made by withdrawing the catheter slowly from the pulmonary trunk to the right ventricle. (Fig. 3.) In two patients it was not possible to pass the catheter into the pulmonary trunk at the initial catheterization. In these patients, clearness of the lung fields in roentgenograms and the character of the auscultatory sounds in the pulmonary valve area militated against the diagnosis of pulmonary hypertension. Pulmonary trunk pressures subsequently obtained at operation confirmed that the diagnosis of pulmonary stenosis was correct.

No significant difference in the saturation of blood samples drawn from various positions on the right side of the heart through the cuvette oximeter was noted in any patient. This finding rendered the possibility of a left-to-right shunt unlikely.

Dye-dilution curves were recorded following injection of Evans blue dye (T-1824) at various sites in the heart and great vessels. In these patients the most significant dye-dilution curves were recorded following injection of dye into the right ventricle and at a site proximal to the right ventricle, either the right atrium or the venae cavae. In cyanotic patients, and especially when there is a right-to-left shunt at the atrial level, a variation in the oxygen saturation of systemic arterial blood frequently occurs. (Figs. 3 and 4.) This is usually related to the respiratory cycle and is probably due to a differing relative magnitude of shunt across the defect associated with changes in the intrathoracic pressure. It is of some practical importance that this variation in oxygen saturation may severely distort the dye-dilution curve recorded oximetrically. However, it is almost always possible to recognize the first appearance of dye with considerable accuracy. (Table III.) The dye-dilution curves recorded following injection into the right ventricle had normal or prolonged appearance time (Table III), indicating that the blood followed a pathway through the lungs and that no right-to-left shunt existed at ventricular level. The dye-dilution curves recorded following injection of dye proximal to the right ventricle had abnormally short appearance times and abnormal initial deflections, indicating that blood shunted from right to left through an interatrial communication. (See Figure 4.)

In Case IX, studied early in this series, the dilution curves were interpreted incorrectly. This patient was referred for cardiac catheterization with a diagnosis of pulmonary stenosis and atrial

* In this laboratory the oxygen content of pulmonary vein blood (cc./L.) for a patient breathing room air is taken to be: $C_{pv_{O_2}}$ = (98 per cent of oxygen capacity + 0.3) × 10.

septal defect. When dye was injected into the right ventricle, a right-to-left shunt of 18 per cent was demonstrated but a larger right-to-left shunt (48 per cent) was found when dye was injected into the superior vena cava. These curves were taken to indicate the presence of evidence of tricuspid insufficiency was demonstrated in addition to an atrial septal defect. It was considered after these findings that the appearance of shunted blood following injection into the right ventricle was due to regurgitation of blood through the tricuspid orifice. In retrospect, more attention should have been paid to the greater magnitude of the shunt from the superior vena cava than from the right ventricle.

TABLE II

INTRACARDIAC PRESSURES, ARTERIAL OXYGEN SATURATION DATA, BLOOD FLOW AND SHUNT VALUES IN 10 CASES OF PULMONARY STENOSIS AND INTERATRIAL COMMUNICATION

Case No.	Age (yr.)	Sex	Pressures (mm. Hg)				Blood O_2 Capacity*	Arterial Oxygen Per cent Saturation (Van Slyke)		Blood Flow L./minute (air)		R-L Shunt† Per cent of Systemic Flow
								Patient Breathing				
			Right Atrium	Pulmonary Trunk	Right Ventricle	Radial Artery		Air	100 Per cent O_2	Pulmonary	Systemic	
I	21	M	15/8	6/4	200/17 to 240/15	118/78	30	66	74	1.6	4.2	62‡
II	19	F	13/2	22/6	157/10	109/68	22	86	93	4.6	8.2	44
III§	5	M	8/6	13/7	105/4	105/58	22	80	...	1.4	3.3	57
IV	13	F	7/2	12/8	129/11	128/70	22	90	99	3.3	4.5	25
V	5	M	10/5	.....	205/10	.....	32	63‖	76‖	...	...	Large¶
VI	22	M	13/8	.....	197/14	156/113	31	70	79	...	...	57**
VII§	3	F	12/9	17/15	129/12	80/50	22	57	71	...	...	62**
VIII	18	F	9/4	11/8	196/9	121/87	23	79	...	...	...	44**
IX	23	M	7/4	8/3	187/7	109/71	34	79	88	1.8	4.0	55
X	23	M	10/4	10/3	91/8	124/64	23	86	98	3.8	5.8	35

* Volumes O_2 per 100 cc. blood.

† Shunt at atrial level.

‡ Flow, shunt and saturation values obtained while the catheter tip lay in the pulmonary artery (see legend to Figure 3).

§ Studied under anesthesia.

‖ Saturations by earpiece oximeter.

¶ From inspection of dye-dilution curves.

** Shunts calculated on the basis of oxygen-saturation data.

ventricular septal defect in spite of a considerable difference between the pressure in the right ventricle and the systemic arterial system. A pulmonary valvotomy was carried out but the patient subsequently died. At necropsy the ventricular septum was found to be intact but

Pulmonary valvotomy was carried out by Dr. J. W. Kirklin in all except one of the patients. Case x was advised to undergo operation

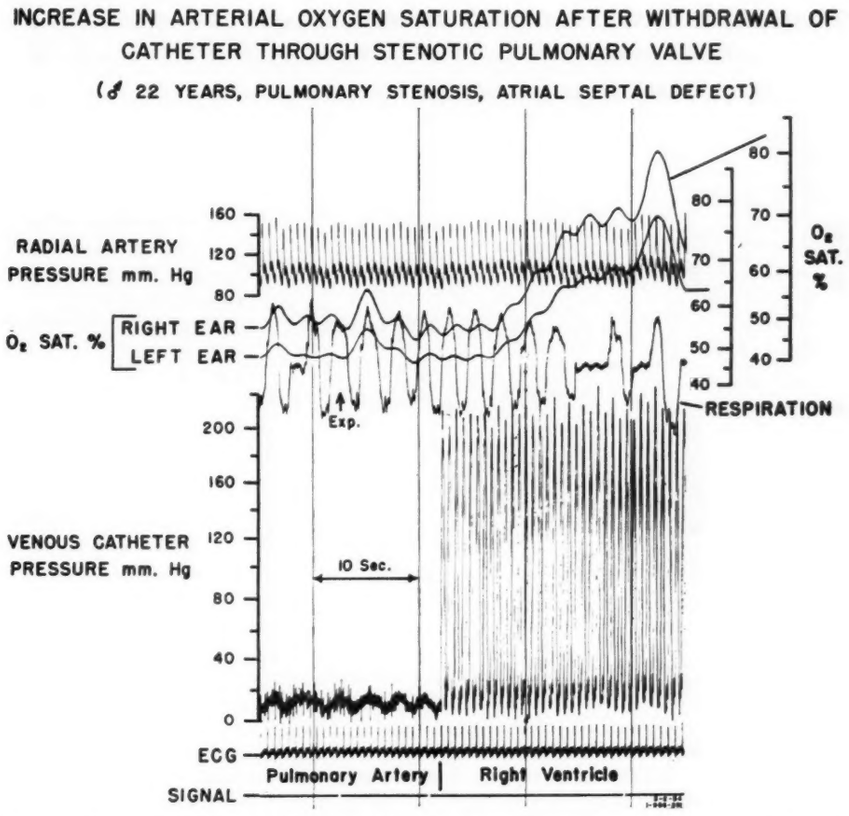

FIG. 3. Case I. Section of photographic record demonstrating the presence of pulmonary stenosis and the increase in oxygen saturation of systemic arterial blood consequent on the movement of a No. 6 catheter from the pulmonary trunk to the right ventricle while the patient was breathing room air. From above downward the record shows the right radial artery pressure, systemic arterial oxygen saturation as recorded by oximeters on right and left ears, the respiration, the pressure in the pulmonary trunk and in the outflow portion of the right ventricle, and the electrocardiogram. At the first break on the signal line the catheter was withdrawn slowly from the right pulmonary artery, and at the second signal it lay just above the pulmonary valve. Without further manipulation the catheter tip passed over a distance of less than 1 cm. into a zone of high pressure. Note the abrupt change in pressure, which indicates the presence of a valvular type of stenosis. The systemic arterial oxygen saturation as recorded by earpiece oximeters shows rhythmic fluctuations of the same frequency as respiration. When the catheter lay in the pulmonary artery, the arterial saturation ranged between 50 and 55 per cent. About six seconds after the catheter passed into the right ventricle the arterial oxygen saturation rose rapidly to approximately 70 per cent and the respirations slowed and became irregular. The systemic shunt and pulmonary flow values and the magnitude of the right-to-left shunt, all calculated while the patient breathed 100 per cent oxygen, were 1.8 L. per minute, 4.2 L. per minute and 57 per cent, respectively, when the catheter lay in the pulmonary trunk; and 2.4. L. per minute, 4.0 L. per minute and 40 per cent, respectively, when the catheter lay in the right ventricle. In this case and also in Case VII the size of the catheter (diameter 1.9 mm.) must have reduced the orifice of the pulmonary valve materially and increased the magnitude of the right-to-left shunt. In Case I, when breathing 100 per cent oxygen, the arterial saturations were 76 per cent, and 87 per cent by Van Slyke analysis when the catheter (diameter 1.9 mm.) lay in the pulmonary trunk and in the right ventricle.

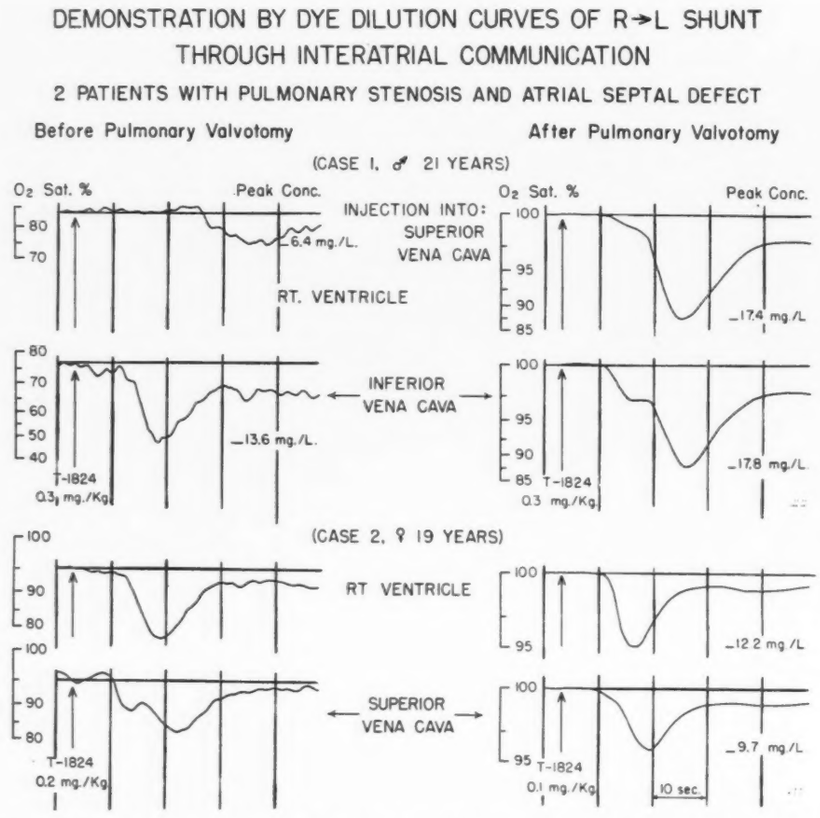

FIG. 4. Dilution curves recorded by earpiece oximeter following injection of T-1824 at the sites indicated in the center of the figure, before and after pulmonary valvotomy in Cases I and II. The oxygen saturation scales to the left of each curve are a relative index of the sensitivity of the oximeter used on the different occasions. The values for peak concentration of dye (to the right of each curve) were obtained from a dilution curve for radial artery blood which was recorded simultaneously by means of a cuvette oximeter. This instrument, but not at present the earpiece, can be calibrated in absolute values of dye concentration. The instant of injection and the amount of dye injected are indicated by the vertical arrow for each curve. The preoperative curves (to the left of the figure) show spontaneous fluctuations in oxygen saturation of considerable magnitude due to variations in the volume of the right-to-left shunt, which interfere with an accurate interpretation of the curves. Note, however, that in both patients the instant of first appearance of the dye is much earlier when dye is injected into the inferior or superior vena cava than when the injection is made into the right ventricle, this fact localizing the site of the right-to-left shunt to the atrial level. In both patients the curves are indicative of right-to-left shunts of large magnitudes. In the right panel are curves recorded following pulmonary valvotomy. Note the absence of spontaneous fluctuations in oxygen saturation, but in both patients an initial break still remains on the build-up portion of the dilution curve, indicating the presence of a small right-to-left shunt. Note also in Case I that the magnitude of shunt from the inferior vena cava exceeds that from the superior vena cava, a phenomenon frequently seen in cases with right-to-left shunt through an interatrial communication.

but he deferred treatment and died suddenly about one month after returning home. Cases VI, VII and IX died shortly after operation.[23] (Fig. 5.) Studies were carried out during the operation in all except one of the patients who underwent operation. These studies (Table IV) show a fall in right ventricular pressure following valvotomy. The findings in this series agree with those of Soulié and his associates[24] in that normal pressures are not usually obtained. As noted by Kirklin and associates[23] the results of these operative studies are not strictly comparable with the results of postoperative cardiac catheterization. The immediate postvalvotomy right

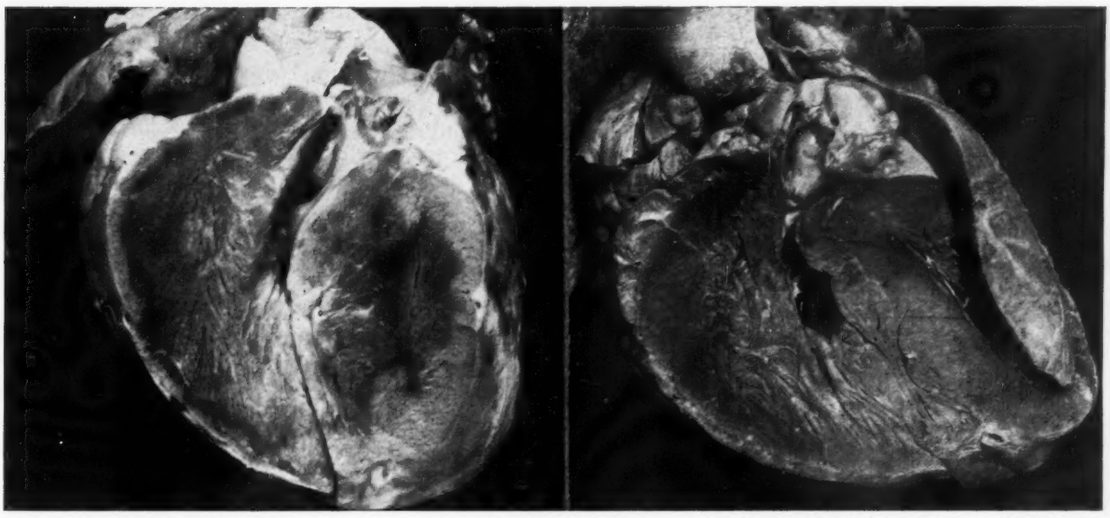

FIG. 5. The hypertrophied right ventricle and outflow tract of the hearts in Case VI (right) and Case VII (left). In Case VII a satisfactory pulmonary valvotomy had been accomplished but the patient succumbed to a respiratory infection (Case VI of Kirklin and associates[23]). This patient had a true atrial septal defect—valve-incompetent foramen ovale—but no left-to-right interatrial shunt was demonstrated at cardiac catheterization. Note in Case VI the unrelieved infundibular stenosis which was considered to be responsible for the patient's death. This patient had a valve-competent patent foramen ovale and no left-to-right shunt was possible. In this type of case indicator dilution curves allow a precise diagnosis to be made at cardiac catheterization.

ventricular pressures in Cases II and V are much greater than the pressures obtained at postoperative cardiac catheterization five months and one and one-half years later. In the four patients who underwent postoperative cardiac catheterization, reductions in right ventricular pressures of somewhat greater than 50 per cent were obtained. In one of the two patients studied postoperatively by earpiece oximetry, only arterial oxygen saturation was found to be increased. In Case IV the postoperative oximetry study did not show improvement in arterial oxygen saturation. However, she and the other patients who survived the operation noted marked subjective improvement.

TABLE III

TIME COMPONENTS AND MAGNITUDE OF R-L SHUNT CALCULATED FROM DYE-DILUTION CURVES AND DEGREE OF SPONTANEOUS FLUCTUATION IN OXYGEN SATURATION IN TEN PATIENTS WITH PULMONARY STENOSIS AND INTERATRIAL COMMUNICATION (RECORDED BY EARPIECE OXIMETER)

Case No.	Per cent Spontaneous Fluctuation*	Right Ventricle			Proximal Site		
		AT (sec.)	PCT (sec.)	R-L Shunt (%)	AT (sec.)	PCT (sec.)	R-L Shunt (%)
I	8.7	23.0	32.5	None	6.9	35	71
II	12.3	9.6	16.4	None	6.9	19.4	44
III	4.5	4.1	9.2	None	3.0	10.3	51
IV	7.0	7.3	14.7	None	5.5	17.0	20
V	4.6	15.2	23.0	None	5.9	30.5	49
VI	3.5	....	....	.....	5.0	21.9	58
VII	1.3	10.2	15.8	None	2.7	16.4	55
VIII	4.0	....	....	.....	8.5	14.2	62
IX	5.5	8.2	28.0	18†	6.0	32.0	48
X	7.4	10.9	18.4	None	6.7	20.8	41

* Spontaneous fluctuation in oxygen saturation associated with the respiratory cycle; difference between the maximal and minimal values for oxygen saturation per cent obtained from a representative portion of record.

Time components:[21]

AT = Appearance time.

PCT = Peak concentration time.

Per cent R-L shunt = R-L shunt calculated as per cent of systemic flow.[22]

† See text for comment.

COMMENT

Patients who have pulmonary stenosis and interatrial communication and who are cyanotic may resemble patients with tetralogy of Fallot in their clinical manifestations. Selzer and his group[1] and Johnson and Johnson[25] stated that pulmonary stenosis with interatrial communication is fairly common as a cause of cyanotic congenital heart disease, probably next in importance and frequency to tetralogy of Fallot among cases of cyanotic congenital heart disease with polycythemia and clubbing. In this laboratory fifty-one patients who had pulmonary stenosis and intracardiac shunt were studied by cardiac catheterization between 1947 and March, 1954. Seventeen (33 per cent) of these had interatrial communications and intact ventricular septa, of whom ten had arterial desaturation at rest. During this period a

number of patients with cyanotic congenital heart disease have undergone operation without prior cardiac catheterization, the diagnosis having been established on clinical grounds alone.

The entire group of patients with pulmonary stenosis and interatrial communication includes those with pure left-to-right shunt, who resemble patients with uncomplicated atrial septal defect clinically; those with a balanced shunt, who resemble patients with isolated pulmonary stenosis; and those with pure or predominant right-to-left shunt, who resemble patients with tetralogy of Fallot clinically. Some of the discrepant reports in medical literature might be related to this variation in clinical appearance which can be found in patients with the same anatomic abnormalities.

There now appear to be relatively few characteristics which set these patients clinically apart from patients with tetralogy of Fallot, although this opinion is not in agreement with that of Engle and Taussig.[26] McGregor and his group[4] and Joly and his group[5] have discussed the comparative findings in these two malformations. Breathlessness, weakness, cyanosis, cyanotic attacks, squatting and polycythemia were found in both conditions. Selzer and associates[1] indicated that pulmonary stenosis with patent foramen ovale occupied an intermediate place between the tetralogy of Fallot, the most cyanotic lesion, and the Eisenmenger complex, the least cyanotic of the three. They and McGregor doubted, however, whether the degree or time of onset of cyanosis was of any differential value in the individual case.

Our findings would be in general accord with the foregoing opinion and also with McGregor's statement that information about the age of

TABLE IV

INTRACARDIAC PRESSURES RECORDED AT THE TIME OF OPERATION BEFORE AND AFTER PULMONARY VALVOTOMY AND ARTERIAL OXYGEN SATURATIONS OBTAINED THREE WEEKS TO EIGHT MONTHS AFTER OPERATION

Case No.	Studies during Pulmonary Valvotomy							Postoperative Studies					
	Date of Operation	Pressures (mm. Hg)						Date of Study	Pressures (mm. Hg)		Arterial O_2 Saturation Per cent		R-L Shunt Per cent of Systemic Flow
		Before Valvotomy			After Valvotomy								
		Pulmonary Trunk	Right Ventricle	Right Radial Artery	Pulmonary Trunk	Right Ventricle	Right Radial Artery		Right Ventricle	Right Radial Artery	Room Air	100 Per cent O_2	
I	3/8/54	.....	60/17	43/38*	13/9	102/8	131/105	3/23/54	119/17	111/63	90	99.5	20†
II	8/18/52	14/8	125/5	100/70	13/8	110/5	85/65	1/12/53	57/15	110/71	92	99	14†
III	2/12/54	35/20	120/20	110/68	45/38	69/35	119/75	2/20/54‡	.....	.....	87	97	...
IV	9/14/53	28/15	165/5	78/62	27/14	75/5	98/62	10/9/53‡	.....	.....	84	95	...
V	11/18/52	23/12	.....	.....	25/13	122/18	.....	6/10/54	45/12	.....	91	97	15†
VI	7/24/52	34/27	220/33	130/107	28/19	188/18	157/115	§	.....	.....	....	....	...
VII	6/6/52	.....	162/17	.....	30/17	42/19	.....	§	.....	.....	....	....	...
VIII‖	.....	.....	.....	.....	.....	.....	.....	12/28/50	62/12	90/60	87.5	96.8	33
IX	5/15/53	17/11	135/10	70/40	17/10	60/10	70/42	§	.....	.....	....	....	...
X¶	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	....	....	...

* During valvotomy patient had severe hypotensive reaction.
† Per cent shunt estimated from dye-dilution curves.
‡ Earpiece oximetry studies only.
§ Died following operation.
‖ Patient not studied during valvotomy.
¶ Patient deferred operation, died one month after study.
(Note: Cases I, III, VII, VIII, IX and X had valvular pulmonary stenosis only; Case IV had infundibular stenosis only; and Cases II, V and VI had combined valvular and infundibular stenosis.)

onset of symptoms may not be reliable. This is most likely to be true in adults, who may have only vague ideas about the exact time of onset of their symptoms and may have no information regarding possible cyanotic attacks before the onset of persistent cyanosis. In the present group of ten patients cyanosis was stated to have been present at birth or in infancy in eight. In one patient it probably began in infancy. In one patient persistent cyanosis developed at seven years but there was a history of transient cyanotic episodes in infancy.

The location and intensity of the murmur in these ten patients did not seem to be of value in differentiating them from patients with tetralogy of Fallot. The second sound in the pulmonary area was absent in five of these patients and single in the remaining five.

Roentgenographic evidence of reduced blood flow to the lungs is common to both conditions. Concavity in the region of the pulmonary artery segment is more characteristic of tetralogy of Fallot. In a series of twenty-five cases of tetralogy of Fallot confirmed at necropsy, however, Brinton and Campbell[27] found that a small heart with concavity in the area of the pulmonary artery segment had been noted in roentgenograms in only a few cases. They found some prominence in the area of the pulmonary artery segment in at least one patient, and considerable variation in heart size throughout the group. Normal chest x-rays have been noted in both conditions. We consider the roentgenographic findings of great importance in the clinical differentiation of these two groups of patients, despite the occasional case with tetralogy of Fallot with a prominent pulmonary artery and the infrequent case of pulmonary stenosis with interatrial communication in which the pulmonary artery is not well visualized. It is apparent from the pulmonary artery silhouettes in this group of patients (Fig. 1) that there may be considerable variation but the pulmonary artery was visualized in the routine postero-anterior chest roentgenogram in all but Cases III and VI.

The nature of the pulmonary stenosis, as determined at cardiac catheterization, is of interest in relation to the radiologic appearance of the pulmonary artery (Fig. 1) in our cases. In four of the five patients (Cases VII to X) in whom the pulmonary artery shadow appeared prominent, there was pure valvular stenosis. In the fifth patient (Case V) an associated short infundibular zone of stenosis could not be excluded. In three patients (Cases I, II, IV) the pulmonary artery shadow was visualized but was not prominent. One of these had valvular stenosis (Case I) but, in spite of the lack of prominence of the pulmonary artery shadow on the preoperative roentgenogram, definite post-stenotic dilatation of the pulmonary artery was noted at operation. Of the remaining two patients in this group an infundibular stenosis was thought to be present in Case IV and a combined valvular and infundibular stenosis in Case II. In two patients the pulmonary artery shadow was not visualized. In Case III the stenosis was valvular in type and in Case VI was combined infundibular and valvular. Case III had a right-sided aortic arch and in Case VI there was pronounced dorsal scoliosis. Either of these conditions might make visualization of the pulmonary artery shadow difficult.

Anomalies of the subclavian vessels and the right-sided aortic arches are seen frequently in cases of tetralogy of Fallot. Brinton and Campbell[27] found a right-sided aortic arch present in approximately one-quarter of their series of cases. Gordon and his group[28] pointed out that the presence of a right-sided aortic arch strongly suggests overriding of the aorta but noted that this anomaly had never been reported in a case with pulmonary stenosis, atrial septal defect and intact ventricular septum. McGregor and associates[4] state that Mannheimer[29] mentioned such a case but that no details were available.

In one of the cases in the present series (Case III) a right-sided aortic arch was found by x-ray. After catheterization it was not possible to exclude the presence of a ventricular septal defect in this patient, although there was no evidence of a shunt at the ventricular level. Indeed, the absence of a significant difference between right ventricular and systemic arterial pressure was consistent with an interventricular communication. (Table II.) At the time of operation, however, the right ventricular pressure exceeded the systemic pressure before valvotomy and fell considerably after valvotomy, while the systemic pressure actually increased. (Table IV.) These hemodynamic findings indicate that the ventricular septum was intact.

The electrocardiogram in cases of tetralogy of Fallot almost invariably discloses some right ventricular hypertrophy but not the extreme degree of right ventricular hypertrophy that has been reported in some cases of pulmonary

stenosis and interatrial communication with intact ventricular septum.[27] This feature may be of definite differential value, since an electrocardiogram showing evidence of very marked right ventricular hypertrophy would suggest a right ventricular pressure higher than systemic pressure, and hence would favor the inference of an intact ventricular septum. The electrocardiograms in all cases disclosed evidence of marked right ventricular hypertrophy. There were no instances of incomplete or complete right bundle-branch block.

Joly and his group[5] stated that the pulmonary stenosis found in association with an intact ventricular septum is characteristically valvular. In the cases in the present series, three were found to have infundibular or combined valvular and infundibular stenosis. Figure 5 (right) is a photograph of the heart from Case VI taken at necropsy showing combined valvular and infundibular stenosis. Figure 5 (left) is a photograph of the heart from Case VII, a case with purely valvular stenosis. Other pictures of these hearts have been published previously by Kirklin and associates.[23]

Use of currently available cardiac catheterization technics makes it possible to arrive at a correct diagnosis in patients with pulmonary stenosis and right-to-left shunt through an interatrial communication. The presence of pulmonary stenosis can be demonstrated when the catheter is passed through the pulmonary valve.[23] If the withdrawal of the catheter from the pulmonary artery through the pulmonary valve to the right ventricle is well controlled, it is frequently possible to identify a zone of intermediate pressure which indicates the presence of an infundibular stenosis. If no intermediate zone is found on slow and careful withdrawal, the stenosis is likely to be valvular but combined infundibular and valvular stenosis may be present in such instances.

The localization of intracardiac defects at cardiac catheterization depends either on the demonstration of arterialization in a cardiac chamber or on the successful manipulation of the catheter through the defect. When a pure right-to-left shunt exists, the site of the defect can be determined with certainty only if the catheter passes through it. Even then it is not possible to be certain that this defect is the site of the right-to-left shunt. In a case of combined atrial and ventricular septal defect with pulmonary stenosis and cyanosis studied recently in this laboratory, a left-to-right shunt was found at the ventricular level, while a right-to-left shunt at the atrial level was demonstrated by the dye-dilution method.[30]

The recent application of the technic of selective injections of T-1824 into the chambers of the heart and great vessels has been of great value in the solution of this problem.[20,31] Even small right-to-left atrial shunts in the presence of large left-to-right shunts have been recognized and quantitated by this method.[32] In seven of the ten patients in this series (Table III) selective dye injections indicated the site of the right-to-left shunt. In a number of these cases a certain diagnosis would not otherwise have been made.

The hemodynamic mechanisms responsible for the direction of interatrial shunts in the presence of pulmonary valve stenosis have not been completely elucidated. The size and nature of an interatrial communication may influence the direction of a shunt across it. Of more immediate importance, reversal of the usual interatrial pressure gradient has been demonstrated by Brecher and Opdyke[33] to be associated with right-to-left shunting of right atrial blood. The question remaining unanswered is the cause of this reversal of the interatrial pressure gradient. The patients included in the present study showed no evidence of cardiac failure, and records of the right atrial pressure did not indicate the presence of tricuspid insufficiency. The magnitude of the right ventricular pressure did not correlate with the magnitude of the shunt.

In patients who have pulmonary stenosis and interatrial communication the cardiac malformations are, at the present time, potentially curable. The pulmonary stenosis, if it is not a long infundibular tract, can be corrected. The atrial communication can be closed. Because such corrective surgery is available, many authorities have urged that these patients be treated by pulmonary valvotomy and not by a shunt operation. Gøtzsche[34] mentioned four patients with pulmonary stenosis and interatrial communication who were treated by shunt operations. In one of these patients congestive failure developed two years postoperatively. This patient was subsequently greatly improved by pulmonary valvotomy.

Brock and Campbell[35] mentioned three similar patients, children with pulmonary stenosis and intact ventricular septum who had undergone a shunt operation and who were

in a state of cardiac decompensation when Brock carried out pulmonary valvotomy. One patient died after operation but the remaining two subsequently underwent surgical repair of the artificial shunt and were markedly improved. All of the nine patients reported in this series who were treated surgically underwent pulmonary valvotomy. Two of these patients died in the postoperative period (Cases VI and IX, Kirklin and associates[23]). A further patient (Case IX of this series) died of intractable bleeding forty-eight hours after operation. The remaining six patients showed differing grades of improvement, but a residual right-to-left shunt was probably present in all cases. Certain individuals might be benefited if the interatrial communication were to be closed.

SUMMARY

1. Clinical and hemodynamic data have been presented in ten cases of pulmonary stenosis and interatrial communication with cyanosis. The clinical similarity between these patients and those with tetralogy of Fallot was noted.

2. Of the ten patients, cyanosis was stated to have been present in eight at birth or in infancy and it probably began in infancy in one other. In the remaining patient transient cyanotic episodes were noted in infancy and persistent cyanosis started at seven years of age.

3. Considerable variation was noted in the cardiac shadow on x-ray examination. The pulmonary artery shadow was visualized in eight of the ten patients on the routine anteroposterior roentgenogram of the chest. It was prominent in five patients.

4. Three of the patients had combined valvular and infundibular stenosis. Six had valvular stenosis only, and one had infundibular stenosis only.

5. One patient had a right-sided aortic arch. To our knowledge this is a very rare finding in a patient with pulmonary stenosis, interatrial communication and intact ventricular septum.

6. Systemic blood flow was greater than pulmonary flow in each case. In five patients the right-to-left shunt was 50 per cent or more of systemic flow.

7. The technic of selective injections of T-1824 was of great value in demonstrating the existence and localizing the site of the right-to-left shunts in the absence of any shunt from left to right.

Acknowledgment: The authors acknowledge the criticism and valuable suggestions offered by Drs. H. B. Burchell, J. E. Edwards and E. H. Wood.

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Hemodynamic Changes in the Bulbar Conjunctival Capillary Bed of Subjects with Hypertension Associated with "Cushing's Syndrome" or Pheochromocytoma*

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IT has been established that individuals with hypertensive vascular disease display certain functional and morphologic changes in the capillary bed of the bulbar conjunctiva.[1,2] These are (1) vasoconstriction of the minute terminal arterioles and metarterioles; (2) increased reactivity of these vessels and the precapillary sphincters to topically applied epinephrine; (3) reduction in the velocity of peripheral blood flow and (4) a prominent change in vascular topography, namely, elongation, coiling and tortuosity of the true capillaries, particularly of their distal and venular portions, including the smaller collecting venules. These abnormalities do not all occur together in normal individuals and in patients with various normotensive diseases, but certain of the phenomena mentioned may be observed in a variety of conditions. For example, vasoconstriction was noted in subjects with rheumatoid arthritis and in cases of hyperglobulinemia, in these instances associated with increased metarteriolar reactivity to epinephrine. Approximately 8 per cent of normal individuals show minimal (Grade I to Grade II) elongation and coiling of the true capillaries. Thus no single observed peripheral vascular phenomenon can be described as "characteristic" of hypertensive vascular disease. It is only when all features observed in the hypertensive capillary bed were considered together that their unique association in this condition becomes apparent.

Within the past two-year period we have examined the conjunctival capillary bed in five cases of hypertension associated with Cushing's disease, three resulting from unilateral adrenal cortical adenomas and two from bilateral adrenal cortical hyperplasia. In addition, observations have been made in three hypertensive individuals proved by operation to have large functional pheochromocytomas. It is the purpose of this report to describe and compare the peripheral vascular changes of each entity; and to compare the findings with those previously noted in subjects with "essential" hypertensive vascular disease.

METHODS

As in previous reports, the bulbar conjunctiva of the individuals was examined with the standard type of slit-lamp microscope and slit-lamp illumination.[1] Subjects were seated before the instrument, and the head held relatively firmly in a combination chin-rest and forehead support, with gaze directed at a point light source flashing intermittently to facilitate fixation of the eye. After examining both the temporal and medial conjunctivas at magnifications of 47 × and 60 × in order to rule out conjunctival disease, the general anatomy and topography of the peripheral circulatory system was scrutinized. In most instances, photomicrographs were taken at 47 × with 35 mm. film. The over-all velocity of blood flow in the peripheral vessels was estimated in comparison with that observed in normotensive subjects without disease. The occurrence and degree of spontaneous vasomotor activity, as evidenced by speeding up and slowing of the blood column in the true capillaries, with narrowing and widening of the blood column at the precapillary region, was recorded in each individual.

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Because of the irregular changes in duration of the open and closed phases within capillary vessels, a subjective impression was obtained concerning the degree of vasomotor activity without attempting precise timing of the duration and frequency of the various phases in representative vessels. Reactivity to topically applied epinephrine was determined by applying solutions of various concentrations into the conjunctival sac, closing the patient's eye for a period of thirty seconds, then observing vessels previously studied for a period of one to two minutes. Beginning with concentrations of 1:800,000, progressively stronger solutions of 1:400,000, 1:200,000, etc., were employed at intervals of three to four minutes until a concentration was found at which "threshold" narrowing occurred in the selected precapillary vessel segments. As with the observations on the velocity of blood flow, this arbitrarily selected end-point has proven useful as a criterion for measurement of reactivity to a vasoconstrictor drug. In studies of over fifty subjects followed for a period of more than two years, the reactivity thus established has been found not to vary more than the standard error described previously.[2]

TABLE I

HYPERTENSIVE VASCULAR DISEASE

	Normal Subjects (125)	Essential Hypertension (100)	Normotensive Diseases (65)
General nature of peripheral blood flow	Vessels tonic; flow rapid and smooth, no stagnation	Vessels constricted; blood flow slowed, tissue ischemic	Highly variable
Spontaneous vasomotor activity	Grade 1–2 in 25% of cases	Grade 3–4 in 85% of subjects	Usually not seen
Velocity of capillary blood flow	Normal (0.026 mm./sec.)	Greatly reduced (0.011 mm./sec.)	Highly variable (0.004–0.03 mm./sec.)
Coiling, looping and tortuosity of capillaries and venules	Up to Grade 1 in 10% of cases	Grade 3–4 in 65% of cases	To grade 1–2 in 15% of cases
Epinephrine concentration required to produce threshold precapillary narrowing	1:37,000 (standard error, 1:3,700)	1:300,000 (standard error, 1:25,000)	1:315,000 (standard error, 1:32,000, highly variable)

RESULTS

The findings in subjects with hypertensive vascular disease previously described are summarized in Table I, and are compared there with those in normotensive subjects without disease and in normotensive subjects with various diseases. It is apparent that vasoconstriction with augmented spontaneous vasomotor activity, reduced velocity of peripheral blood flow in all peripheral vessels, and elongation, coiling and tortuosity of the capillaries and venules, occurred as an entity only in the subjects with hypertensive vascular disease. In Figure 1 the topographic plan of a normotensive subject without disease is shown. This may be compared to the pattern of the peripheral vascular system of a hypertensive subject without other disease shown in Figure 2. The difference in arrangement of the peripheral vessels is apparent.

Cushing's Syndrome. In Table II are the observations on subjects with Cushing's syndrome. The dysfunctional phenomena previously reported in hypertensive vascular disease are duplicated in subjects with hyperadrenalcorticalism. Figures 2 and 3 demonstrate that both groups also display similarly abnormal topographic arrangement of peripheral capillary vessels. There is elongation and coiling of the capillaries and venules, probably more noticeable in the venular portions of the individuals with Cushing's disease than in the hypertensive subjects without other disease states. The findings in the (conjunctival) capillary bed therefore do not permit separation of subjects with "essential" hypertensive vascular disease

from individuals whose hypertension is associated with adrenal cortical hyperfunction.

Pheochromocytoma. In Table III are the data on the patients with hypertension associated with pheochromocytoma. The terminal arterioles and precapillaries are narrowed and the tissues are ischemic. The velocity of blood flow is reduced to approximately the levels at which it is noted in "essential" hypertensive vascular disease and in Cushing's syndrome. A striking difference, however, was the complete absence of capillary and venular elongation, coiling and tortuosity. (Fig. 4.) The anatomy and arrangement of elements in the peripheral vascular system of these patients were quite comparable to those observed in normotensive individuals, with or without any other disease.

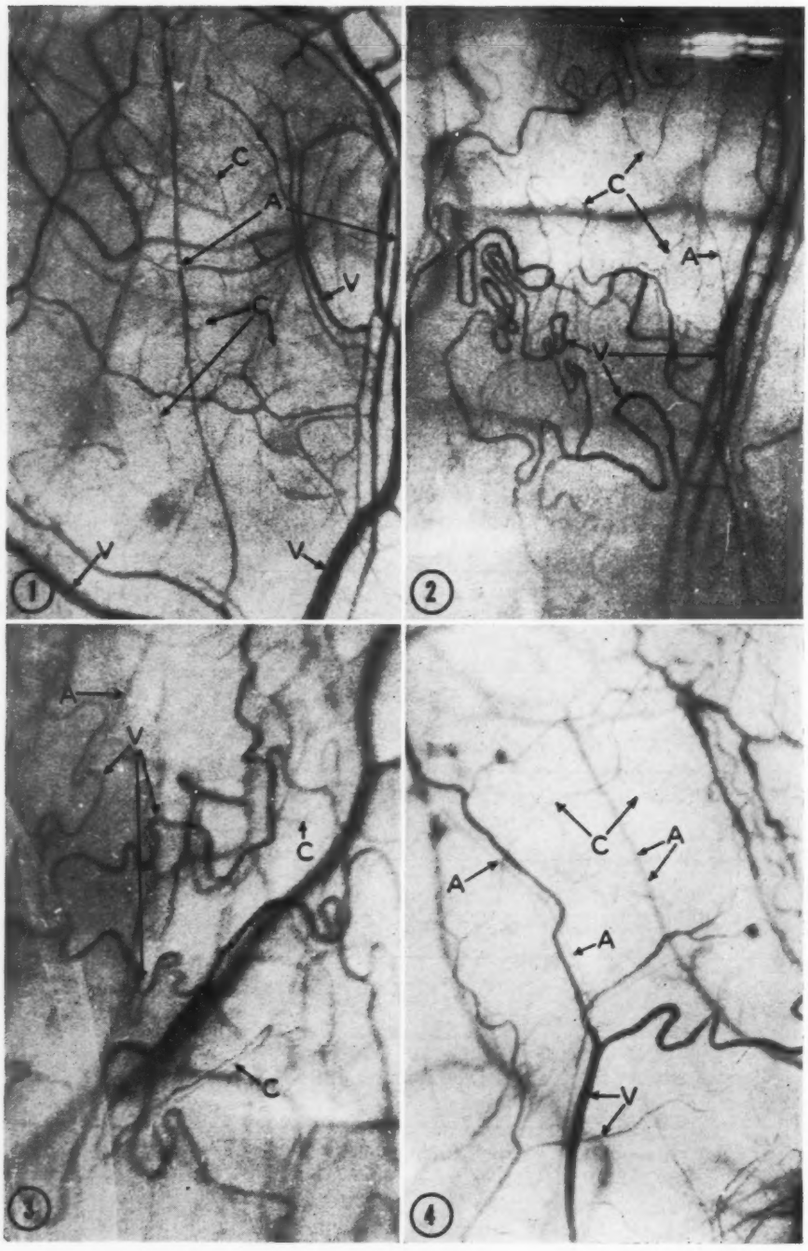
It was possible in patient C. to observe the conjunctival capillary bed with the patient at rest and again during and following a hypertensive crisis produced by massage of the abdominal tumor. At resting blood pressure of 160/105 the capillary bed was ischemic, with moderately constricted arterioles and precapillary sphincters and epinephrine sensitivity of approximately four and a half times the normal range was observed. Vasomotion was minimal, the precapillary sphincters being predominantly narrowed. Within thirty seconds after beginning abdominal massage the blood pressure began to rise, attaining a level of 260/160 in sixty seconds. Coincidentally with the increase in blood pressure, the terminal arterioles and precapillaries were seen to

TABLE II
CUSHING'S DISEASE

Patient	General Aspect	Topography	Epinephrine Reaction (× 1000)	Velocity of Flow
M. M.	Constriction of arterioles Grade 1, otherwise unremarkable	Grade 1 coiling and tortuosity of venular aspects of capillaries	1:200	Slightly reduced
Ch.	Grade 3 constriction with moderate ischemia	Grade 3–4 coiling and tortuosity of capillaries and venules	1:400	Greatly reduced
Lob.	Grade 3 constriction with moderate ischemia	Grade 3–4 coiling and tortuosity of capillaries and venules	1:400	Greatly reduced
Swe.	Grade 3 constriction and ischemia	Grade 3–4 coiling and tortuosity of venules and capillaries	1:300	Greatly reduced
Har.	Grade 3 constriction and ischemia	Grade 3–4 coiling and tortuosity of all small vessels	0:400	Greatly reduced

TABLE III
PHEOCHROMOCYTOMA

Patient	General Aspects	Topography	Epinephrine Reactions (× 1000)	Velocity of Flow
C.	Slight vasoconstriction	Normal, no abnormalities found	1:100	Normal
M.	Notable arteriolar narrowing, with ischemia	No abnormalities found	1:200	Slightly reduced
Mo.	Moderate amount of narrowing, with ischemia	No abnormalities found	1:200	Slightly reduced



HUMAN CAPILLARY BED

FIG. 1. The normotensive subject shows absence of arteriolar constriction and relatively straight, patent capillaries and venules. (A, arterioles; C, true capillaries; V, venular portions of capillaries and collecting venules.)

FIG. 2. Essential vascular hypertension is accompanied by narrowed arterioles, fewer patent capillaries, and coiling, tortuosity and elongation of venular capillary segments and collecting venules.

FIG. 3. In Cushing's syndrome, the arterioles (in this case) were so narrowed that they are not readily noted in the photomicrographs. The capillaries and venules display prominent tortuosity and coiling, with elongation of the venular segments, very similar to that seen in essential hypertension.

FIG. 4. The capillary bed in pheochromocytoma has narrowed arterioles and few capillaries per unit of tissue; but the bizarre topographic abnormalities of Cushing's syndrome and essential hypertension are not observed.

constrict, almost to complete closure. At this time application of epinephrine of 1:800,000 produced complete closure of all of the patent arterioles. This represented a three to fourfold increase over the previously existing threshold level to twelve times the normal reactivity of arterioles to topically applied epinephrine. The blood pressure remained elevated and these findings persisted in the conjunctival capillary bed for approximately two and one-half minutes. The blood pressure then fell slowly within a period of four minutes to its former level of 160–165/105. During the fall in blood pressure the terminal arterioles gradually widened to resume their former partially constricted state, and blood flow increased to its previous speed. When the blood pressure had fallen to the preexisting level of 165/100, the reactivity of precapillaries to epinephrine returned to former levels of but four and a half times the normal value. It was assumed that the visualized vasoconstriction and ischemia were the result of an increase in the amount of epinephrine circulating within the blood stream. The augmented vascular reactivity to applied epinephrine probably represented a summation of the effects of the increased intravascular epinephrine with that applied to the outside of the arterioles and precapillaries.

Patient C. was explored surgically within a week after these observations and a large pheochromocytoma of the left adrenal gland was removed. The patient's blood pressure returned to normal levels. Observations of the conjunctival vessels seven days after operation and at least three times in the two-year interval following operation have demonstrated a normal topographic vascular arrangement and velocity of blood flow, with a reactivity of terminal arterioles and precapillary sphincters that is well within the usual range of normotensive individuals.

COMMENTS

It is apparent that the abnormalities present in the peripheral vessels (of the conjunctiva) in essential hypertension are similar to those present in like vessels of subjects with high blood pressure accompanying "Cushing's" disease.[2] In cases of pheochromocytoma, on the other hand, even though a persistent hypertension is present, the peripheral vessels in certain regards display a considerably different state. The arterioles and precapillaries are less hyperreactive to topically applied epinephrine, and there may be rapid variation in the degree of such vascular reactivity associated with the transient rise and fall in blood pressure produced by manual compression of the tumor mass (Patient C.). This latter picture contrasts sharply with the stability of epinephrine hyper-reactivity present in essential hypertension and in Cushing's disease.

A third and most outstanding difference noted was the complete absence in the patients with pheochromocytoma of the capillary coiling, tortuosity and elongation that were prominent features of the peripheral vascular bed of essential hypertensive and of hypertensives with Cushing's disease. The absence of this phenomenon in cases with adrenal medullary tumor, and its presence in hyperadrenal corticalism, suggests that development of such pathologic changes in the capillary bed may depend, at least in part, on excessive adrenal cortical activity.

The physiologic importance of capillary coiling, elongation and (in the venular portion) a widened capillary diameter is not clear. In view of the increased capacity which such changes afford in the single capillary, however, it is conceivable that the capillary bed *per se* might thus be enabled to hold considerably more blood. The increase in blood-holding capacity would reside primarily in the venular side of the peripheral vascular network, in contrast to diminished volume of the terminal arterioles resulting from arteriolar vasoconstriction. Thus the change may represent vascular adjustment to maintain the volume of blood within capillary bed elements. A second and equally plausible explanation of the increased capillary length and coiling may be based on arteriolar-capillary pressure relationships. Although the increased arterial blood pressure in hypertension is thought to be expended chiefly in the smaller arteries and the larger pulsatile arterioles, there is recent evidence that a portion of the increased pressure is transmitted peripherally to the metarterioles and their capillary offshoots.[3] With such an increase in the intracapillary pressure, conditions would greatly favor outward filtration of fluid and electrolytes, particularly in the proximal portion of the true capillaries. The accumulation of excess interstitial fluid as a result of such hydrostatic changes might be prevented by a corresponding increase in the factors which facilitate inward filtration of interstitial fluid, a

return to the intravascular space. The increase in length and in surface area afforded by the coiling and tortuosity (all of which occur chiefly in the distal portions of the capillaries where inward filtration probably predominates) may represent changes designed to increase greatly the potential ability to mobilize fluid from outside of the vascular bed. Thus although the rate of outward filtration at the proximal capillary segment might be theoretically increased, the expansion of surfaces for inward filtration in the more distal portions of the capillaries would maintain normal intravascular-extravascular fluid volume relationships.

CONCLUSIONS AND SUMMARY

1. The capillary bed in the bulbar conjunctiva was studied in eight patients with hypertension associated with pheochromocytoma or "Cushing's syndrome" (hyperadrenalcorticolism).

2. When compared with the findings in essential hypertension, the peripheral vascular system in hypertension caused by pheochromocytoma shows a similar but less notable vasoconstriction, less hyper-reactivity to epinephrine and complete absence of capillary and venular coiling, tortuosity and elongation. During a hypertensive crisis in one case, extreme increase in vasoconstriction, tissue ischemia and reactivity to epinephrine was observed, in contrast to the stability of the vascular status in essential hypertension.

3. Subjects with "Cushing's syndrome," on the other hand, display a pattern of vascular topography and response in the capillary bed that could not be differentiated from that found in essential hypertension.

4. The possible significance of these observations is discussed

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Kidney Biopsy in Acute Anuria*

With a Case of Acute, Bilateral Cortical Necrosis

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AMONG the various disorders of the kidney in which the kidney biopsy method has been employed, its usefulness has been demonstrated particularly in acute anuria. Evidence of this appears in Brun's findings based on kidney biopsies obtained in twelve patients with acute anuria (acute tubulo-interstitial nephritis).[3] The most essential histologic changes observed by Brun were: (1) The glomeruli were normal. (2) The proximal tubules presented low flattened epithelium and, in some cases, dilatation. (3) The distal tubules and the ascending part of Henle's loops were dilated, showing flattening of the epithelial cells. (4) In circumscribed areas the protoplasm of the epithelial cells in the proximal tubules sometimes showed so-called "hydropic" changes. Brun[3] also often found coexisting degenerative and regenerative (mitoses) processes in the tubular epithelium. (5) There were interstitial changes consisting of focal or diffuse edema with or without cellular infiltration. (6) Finally, the presence of hemoglobin-stained casts in the distal tubules, Henle's loops and collecting ducts, were noted. Tubular necroses were not observed. Brun has pointed out that interstitial changes play a much more important part than has been supposed by previous investigators. His findings also support the criticism of the term "lower nephron nephrosis" since, as pointed out by Oliver, MacDowell and Tracy,[19] among others, the infection is localized not only to the "lower nephron" but also, and perhaps chiefly, to the proximal tubules. The fact that postmortem autolytic processes are most pronounced in the proximal tubules may be the reason why the degenerative changes in the tubules have hitherto been underestimated.

As is known, tubulo-interstitial nephritis represents a very polymorphous group of diverse etiology; this also appears from Brun's series. In spite of this, it has not been possible to find histologic dissimilarities corresponding to the different etiologies.

In the three cases to be recorded the histologic findings were very different and, in at least two of the patients, were undoubtedly so characteristic of the underlying causes that a report of the cases might be of interest.

METHOD

The kidney biopsies were performed by the Iversen and Brun method,[12] and five biopsies in all were obtained in the three patients. Because of the presence of impaired renal function, the biopsies were not preceded by intravenous pyelography. Renal function was studied by twenty-four hour endogenous creatinine clearance and determinations of serum urea and serum creatinine. The kidney biopsies were uncomplicated. The authors had an opportunity to examine the sites of puncture at subsequent autopsies of two of the patients; nothing abnormal was observed.

CASE REPORTS

CASE 1. A thirty-three year old man, previously in good health, was assaulted by hooligans on August 20th, 1953, at 1 A.M. and incurred a bilateral fracture of the mandible. During the next three days he had headaches, nausea, dizziness and fever but was able to come in a taxi for treatment of the mandibular fractures.

Having become confused during the preceding night, he was admitted to the neurosurgical department on the morning of August 23 (three and a half days after the assault) in a completely unconsciousness state. On admission he was in shock. The pulse was impalpable, the

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action of the heart inaudible, the blood pressure 80 mm. Hg, and cyanosis of the lips and the finger tips was noted. Breathing was intermittent and gasping, and copious secretion in the respiratory tract was observed. In view of the possibility of an intracranial, extracerebral hemorrhage, surgery was performed, two holes being drilled on either side of the skull. No intracranial hemorrhage was found however, During the days that followed the patient was dull and semi-conscious, had respiratory rales and was cyanotic. On August 23 the output of urine was 250 ml., on August 24 (the day following surgery) it was 450 ml. During these twenty-four hours the patient was given 3000 ml. of fluid. The next day (August 25) the output of urine had fallen to 100 ml., the patient became increasingly restless, the blood urea level had risen, and acidosis and rising blood pressure were noted; further, atelectasis of the left lung was present. On August 25 the patient was given 50 ml. of a 50 per cent solution of sucrose, as cerebral edema was suspected.

On August 26 the patient was transferred to Department III (Medicine) owing to anuria, uremia and arterial hypertension. He was dull and semi-conscious on admission, though he reacted when spoken to and gave adequate replies. However, he was not oriented in time or place. There was some edema, especially of the legs. The blood pressure was 190/135 mm. Hg; serum urea, 244 mg. per 100 ml.; and serum creatinine, 10.4 mg. per 100 ml. Catheterization yielded only 20 ml. of slightly bloody urine.

At 5 P.M. on the day of admission the patient had an attack of generalized convulsions for about fifteen minutes and then lost consciousness. Ophthalmoscopy showed normal eyegrounds. A neurologist considered that cerebral edema was present and recommended the administration of sucrose. Therefore, for the second time in forty-eight hours the patient was given 50 ml. of a 50 per cent solution of sucrose intravenously.

The next day (August 27) the serum urea had risen to 354 mg. per 100 ml., the serum creatinine to 14.6 mg. per 100 ml., and the oliguria persisted. At 1:30 P.M., that is, after four days in a state of shock, he died; the principal cause of death was presumed to be cerebral edema.

Kidney biopsy had been performed one hour and forty minutes prior to death. The tissue obtained measured about 9 mm. in length (Figs. 1 and 2) and consisted of cortex containing 10 glomeruli, all of which were normal. The epithelium in all proximal tubules and in many distal tubules had undergone pronounced "hydropic" change. In many tubules there were either no nuclei or very few; many of the nuclei present were pycnotic. The cells in the proximal tubules were rather tall, and the lumina were slightly dilated in many areas. As already mentioned, the epithelium in a number of distal tubules showed similar changes, in others it was flattened. A few slightly hemoglobin-stained casts were seen in the lumina of the distal tubules. No inflammatory infiltration, no interstitial edema and no vascular changes were seen. The histological diagnosis was diffuse "hydropic degeneration" and some hemoglobin-stained casts.

Autopsy showed: (1) Three fractures of the mandible had been sustained. (2) Hematomas were present in the pharynx and the larynx and in the subcutaneous tissue on the anterior surface of the neck. (3) Severe edema and pronounced hyperemia of the brain were noted. (4) The kidneys were of normal size with smooth surfaces and normal proportions of cortex and medulla; the cortices were somewhat pale. (5) The lungs showed congestion and edema, and atelectasis of the left lower lobe was present.

In addition to the same changes as were seen in the biopsy, histologic examination of the kidneys at necropsy revealed scattered small interstitial infiltrates of lymphocytes and macrophages in the cortex, which also showed distinct interstitial edema in some areas. Considerable amounts of hemoglobin-stained casts were present in Henle's loops and in the collecting tubules.

Summary and comments: A thirty-three year old man developed deep shock, anuria, uremia, hypertension and edema three days after severe head trauma and died on the seventh day. The principal cause of death was presumed to be cerebral edema. Kidney biopsy and autopsy specimens showed slight acute tubulo-interstitial nephritis and pronounced diffuse "hydropic" tubular changes, especially in the proximal tubules. The latter lesion was probably due to intravenous administration of sucrose.

There is every reason to believe that this patient was overhydrated; this undoubtedly contributed to his death. The autopsy revealed both cerebral and pulmonary edema (both of which, however, could have been due to uremia; the brain edema could have been possibly due also

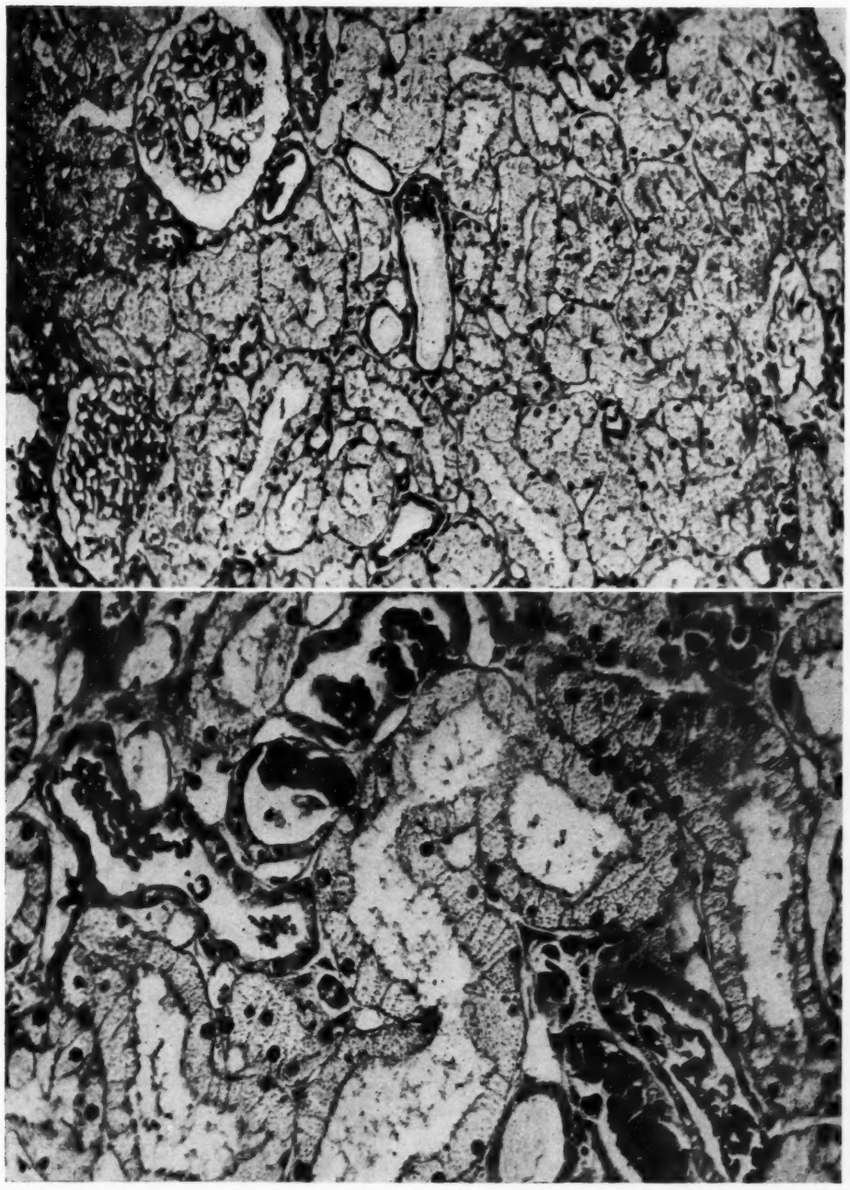


FIG. 1. Kidney biopsy with normal glomeruli, pronounced "hydropic" changes in all proximal tubules (probably due to intravenous sucrose administration) and a few hemoglobin-stained casts in the distal tubuli with flattened epithelium; × 145. (Case 1.)

FIG. 2. Kidney biopsy from the same preparation as Figure 1 showing the same lesions; × 280. (Case 1.)

to the trauma) and hypertension had been present.

The significance of the diffuse so-called "hydropic" changes found in the tubules in this case is not known. They resemble a diffuse form of the change which Brun[3] and others have found in acute, tubulo-interstitial nephritis in more focal areas. Whether it can be considered indicative of an intracellular edema cannot be stated with certainty.

The patient had been given two intravenous injections of sucrose while the renal function was much impaired and oliguria was present. It is known from the literature[1,6,8,10,11,15,16] that, when given intravenously to dehydrate the tissues, especially the brain, sucrose may pro-

duce marked "hydropic" changes in the proximal tubules of the kidney; however, the significance of these changes is not known. With regard to the effect on the renal function of a single injection of sucrose, opinions differ. Joliffe, Shannon and Smith[13] have shown that sucrose injected subcutaneously does not alter the xylose or the urea clearances, whereas it has been shown by Helmholz[10] and Helmholz and Bollmann[11] that the excretion of phenolsulfonphthalein decreases after a single injection. But it does not appear that repeated injections of sucrose in physiologic quantities can give rise to permanent renal lesions.[8,10,11] It is not known whether sucrose may injure tubular cells in a kidney which does not function normally, but it would seem irrational to use sucrose for dehydration in acute oliguria when the organism is unable to eliminate water.

With regard to the renal changes in the present case, they must be considered to have been caused chiefly by the treatment with sucrose and to a lesser degree by acute tubulo-interstitial nephritis (hemoglobin-stained casts and interstitial infiltrates).

Case II. A thirty-five year old woman had been feeling tired and nervous during the past year and a half. In March 1953, she had an infection considered to be pneumonia. Since that time the sedimentation rate had been increasing, and she had become progressively fatigued, nervous and irritable.

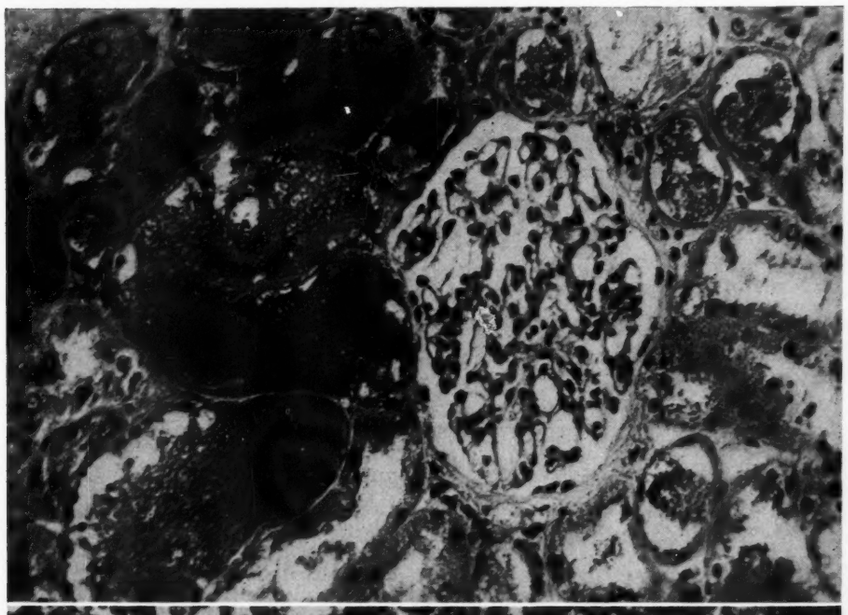
Early in the night of August 18, 1953, she suddenly became ill, feeling very sick with chills, copious diarrheal discharges, profuse vomiting, nausea, headache and lumbar pain radiating into the groin. There was slight vaginal bleeding. She had a fever of 40°C. Four hours after onset she was admitted to Surgical Department I, Kommunehospitalet, for observation for febrile abortion. Gynecologic examination showed that the uterus was enlarged, corresponding to a pregnancy in the eighth week, and there was moderate bleeding. She had not menstruated for two months.

A good deal of medicine had been taken at home, none of which was known to produce hemolysis. When questioned several times both the patient and her husband denied that abortifacients had been taken; their denial seemed trustworthy. Questioning revealed that no one else in their home had become sick following supper.

Catheterization on the morning of August 18 yielded 100 ml. of bloody urine. On examination at 12 A.M. she was neither exhausted nor in shock but had a brownish, icteric, rather mulatto-colored appearance. At this early stage of the disease she already had severe anemia (hemoglobin percentage, 49), and the serum was of a dark reddish brown color (hemoglobin percentage in serum, 11). Marked leukocytosis was present in the peripheral blood (64,000). The blood was examined to determine the cause of the hemolysis but no signs were found to indicate the presence of immune-hemolytic anemia. On the same day the patient was transferred to Medical Department III for uremia (serum urea, 135 mg. per 100 ml.; serum creatinine, 4.9 mg. per 100 ml.).

Kidney biopsy was performed twice on this patient, on the third day of the disease (August 20) and on the ninth day (August 26). Pronounced oliguria was present on both occasions. The specimen of renal tissue obtained on August 20 measured 3 mm. in length (Fig. 3) and consisted of cortex containing three glomeruli in all; these were normal. The proximal convoluted tubules appeared to be normal also. However, the epithelium was comparatively low. and in a few areas the nuclei apparently protruded directly into the lumina which appeared rather wide but hardly dilated. In almost all distal tubules there were coarse grained, distinctly hemoglobin-stained casts which apparently distended the lumina, the epithelium thus being flattened. No inflammatory infiltration was noted, and there seemed to be no interstitial edema. The histological diagnosis was numerous hemoglobin-stained casts in the distal tubules.

The biopsy specimen of the kidney, obtained on August 26, measured about 3 mm. in length (Fig. 4) and consisted of cortex containing four glomeruli, all of which were normal. The epithelium was consistently low in the proximal tubules and very low in the distal tubules; most of the latter had deeply hemoglobin-stained casts which contained remnants of nuclei in some places. There was no definite hydropic change, no tubular necrosis. There were several small interstitial inflammatory infiltrates consisting of lymphocytes and macrophages, very few neutrophil leukocytes and a few plasma cells. Slight interstitial edema was observed in some areas. No vascular changes were noted. The histologic diagnosis was acute tubulo-interstitial nephritis.



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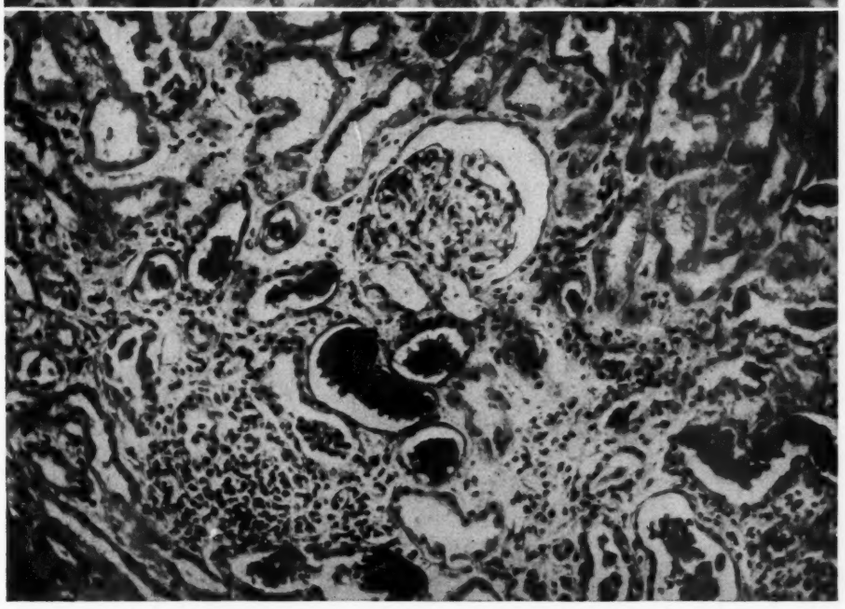

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FIG. 3. Kidney biopsy with normal glomerulus and distal tubuli distended by hemoglobin-stained casts; × 280. (Case II, third day after hemolysis.)

FIG. 4. Kidney biopsy with the same lesions as those shown in Figure 3; edema and slight inflammatory infiltration interstitially; × 145. (Case II, ninth day after hemolysis.)

Chart 1 shows how the oliguria varied from 67 to 122 ml./24 hours for a fortnight; only then did the output of urine begin to increase spontaneously. The urine was dark brown during the first six days of the disease. During the period of oliguria the serum urea rose progressively, the maximum being 468 mg. per 100 ml. on the sixteenth day. The twenty-four hour creatinine clearance was measured daily and was estimated to be 0.2 to 0.7 ml./minute during the period of oliguria. The patient remained conscious, and vomited a good deal. On the eleventh day of illness, as the oliguria persisted, the patient was transferred to the University Medical Clinic in Lund, Sweden (N. A. Alwall) for treatment by dialysis. However, the output of urine began to increase spontaneously from the thirteenth to the fourteenth day of the disease

and slowly rose to very high levels. From the sixteenth day the serum urea began to fall. As the patient's general condition never became serious, it was considered in Lund that hemodialysis was not indicated. On the twenty-fourth day of the disease she was transferred back to Copenhagen. On her return she had developed stomatitis and large conjunctival hemorrhages but was feeling well; towards evening she became restless and anxious, was slightly obtunded, and the pulse was bigeminal. Examination of the blood revealed hypokalemia (serum potassium, 2.7 mEq./L.). Next day (the twenty-fifth day of the disease) an attempt was made to remedy the hypokalemia by the administration of potassium by mouth and by infusion. As the serum sodium (111 mEq./L.) and the serum chloride (91 mEq./L.) showed low values, the patient was

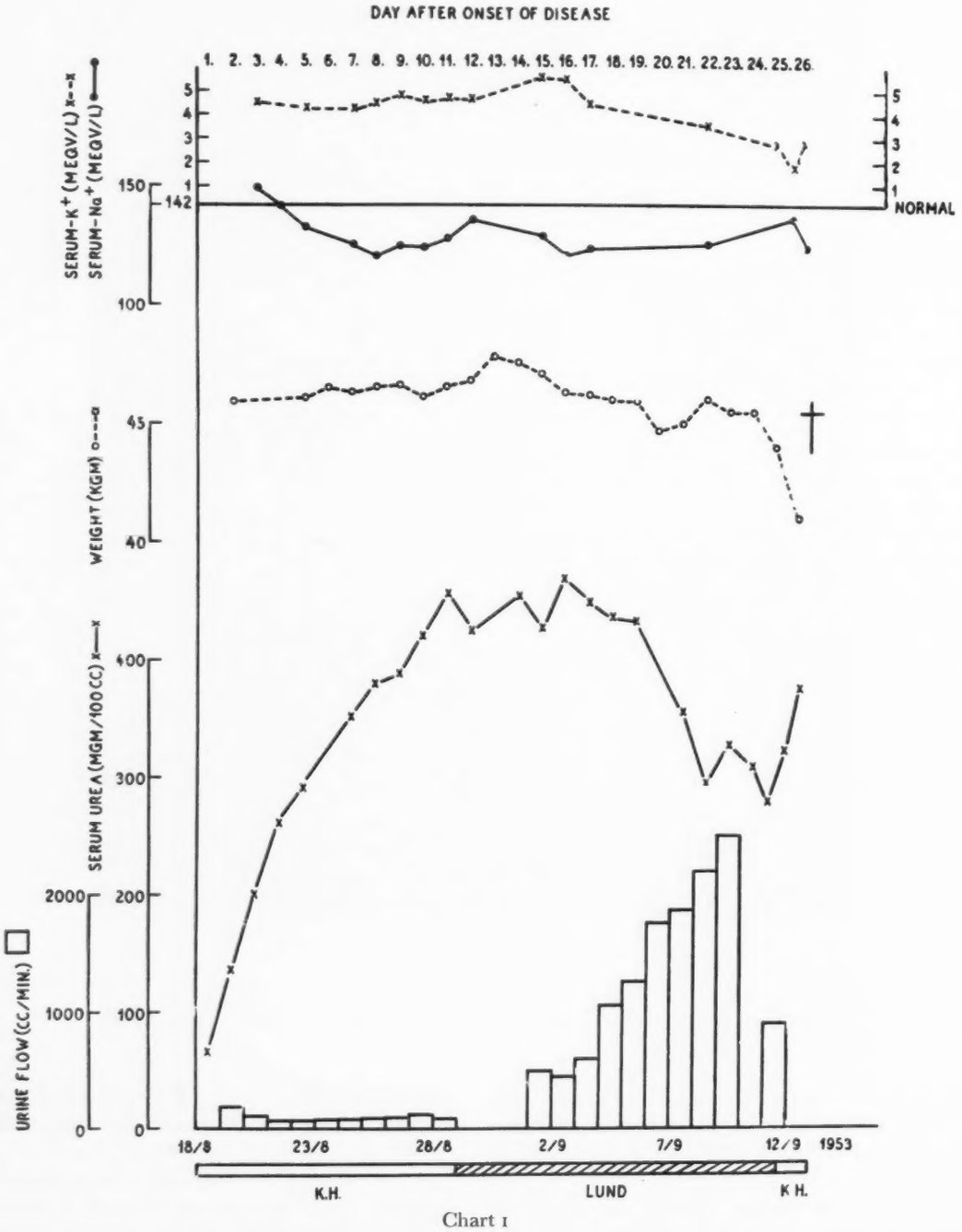

Chart 1

also given a 0.9 per cent saline solution. In the afternoon she developed faint muscular twitchings and at 7 P.M. developed convulsive seizures of the right arm and the right side of the face. Three hours later she died of pulmonary edema.

Autopsy revealed a subarachnoid hemorrhage around the left hemisphere and a small area of encephalomalacia in the left capsula interna. Pronounced acute congestion and edema of the lungs was also noted. The uterus revealed a small intumescence in the mucous membrane, surrounded by hemorrhages; histologic examination revealed decidual tissue, indicating that the patient must have been pregnant. Histologic examination of renal tissue showed numerous hemoglobin-stained casts in the distal tubules, Henle's loops and collecting ducts.

Summary and comments: A thirty-five year old pregnant woman suffered from severe (toxic?) hemolytic anemia with renal failure and oliguria-anuria of thirteen days' duration. The renal function improved during conservative treatment but the patient died on the twenty-sixth day of subarachnoid hemorrhage and localized encephalomalacia. Kidney biopsy and postmortem specimens showed numerous hemoglobin-stained casts in almost all distal tubules.

In view of the sections obtained by kidney biopsy (Figs. 3 and 4), one must consider whether the numerous hemoglobin casts found played a part in the causation of oliguria by blocking the tubules; as already mentioned, both biopsies were performed during the period of oliguria. Later, the patient had a phase of fairly pronounced polyuria. Autopsy specimens of renal tissue still showed many of the casts. This fact suggests that the casts need not necessarily play a part in the oliguria, as one might be inclined to believe.

CASE III. This was a twenty-one year old woman who had been previously in good health. As the result of a local trauma six months before admission, she had a stillborn child about two months before term. Two months before admission the patient had an early abortion. She was not pregnant at the onset of the present disease. Except for an attack of pyelonephritis of short duration, treated at home a year and a half before admission, she had never had symptoms of infection of the kidney.

The patient was admitted to Department III, Kommunehospitalet, on October 13, 1953 because she had not passed urine for four days. The disease had begun rather suddenly on October 8 with bilateral lumbar pain, nausea, vomiting and rise of temperature to about 38°C. There had been no preceding disease, no dysuria, no edema, no disturbances of vision. The patient had not been in contact with toxic substances, had not taken any drugs which might produce renal damage, and there were no signs of hemolysis in the blood.

She was conscious and was not exhausted on admission. Except for moderate bilateral tenderness in the lumbar regions, results of physical examination were normal. Blood pressure was 115/60 mm. Hg. Immediately after admission 20 ml. of slightly turbid urine with a specific gravity of 1.020 was evacuated by catheterization. Microscopic examination of the urine showed a number of erythrocytes, a few leukocytes, epithelial cells and hyaline casts. The patient produced no urine for the next sixteen hours. Cystoscopy sixteen hours later did not show any urine in the bladder. Moderate cystitis was present, and no urine was obtained by ureteral catheterization. No obstruction was found, and direct pyelography revealed nothing pertinent.

On October 14 (the sixth day of the disease) the serum urea was 253 mg. per 100 ml., and the serum creatinine was 12.4 mg. per 100 ml. Serum chloride was 83.3 mEq./L., serum sodium 121 mEq./L. An electrocardiogram showed inverted T waves but laboratory investigations gave otherwise normal results.

Kidney biopsy was performed twice, on the seventh and eleventh days of the disease (October 15 and 19, respectively). The output of urine was low on both days. (Chart II.) The kidney biopsy obtained October 15 consisted of two small tissue cylinders measuring 3 and 5 mm. in length, respectively, the smaller one consisting of cortex, the longer one of medulla. Most of the cortical tissue was necrotic; the interstitium was edematous, in parts markedly infiltrated with blood, and extensively infiltrated with leukocytes. One could discern the shadowy markings of tubules (Fig. 5) in which no nuclei could be observed. However, one end of the cortex specimen contained three glomeruli which were fairly well preserved. The basement membranes showed slightly diffuse hyaline thickening and some contained small hyaline precipitates. The tubules in the circumference of these glomeruli showed fairly marked necrobiotic change, and most of these tubules contained large, hyaline casts which filled the highly dilated lumina.

The medullary tissue showed no necrosis or necrobiosis, and scarcely any increase in interstitial connective tissue was noted. There was no inflammatory infiltration in the medulla. Considerable amounts of hyaline or slightly hemoglobin-stained casts were present in the loops and the collecting ducts, but there were no coarsely granulated, deeply hemoglobin-stained casts like those present in tubulo-interstitial nephritis.

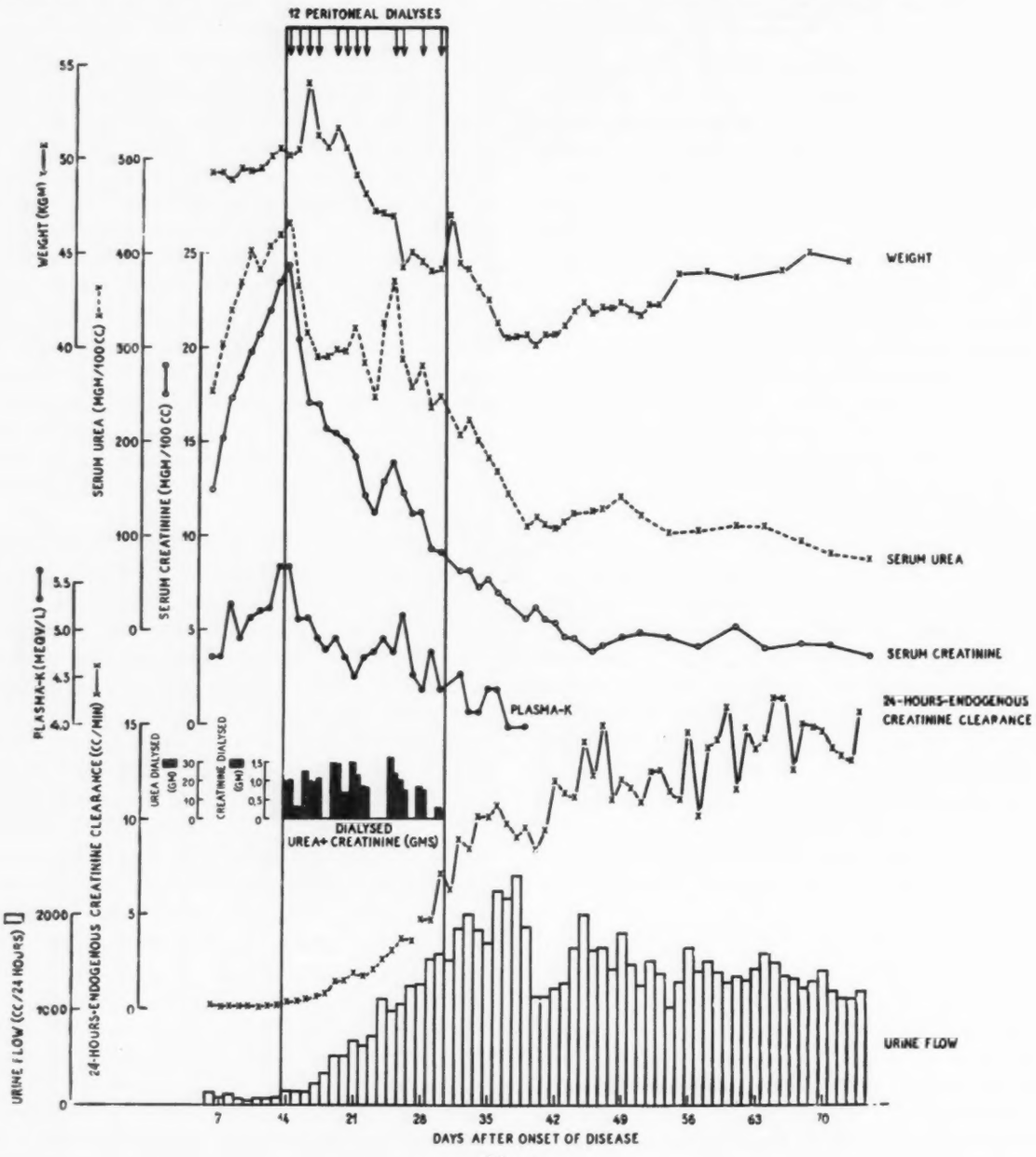

Chart II

The partly necrotic cortical tissue seemed to resemble renal tissue from an ischemic infarct or from the hyperemic border zone of such an infarct. The histologic diagnosis was partly necrotic cortical tissue—tissue from a kidney infarct (?)—medullary tissue with a number of hyaline and slightly hemoglobin-stained casts but without other changes.

The biopsy specimen obtained October 19 measured about 9 mm. in length and consisted of about two-thirds cortex and one-third medulla (Figs. 6, 7, 8, 9). About 4 mm. of the outermost portion of the cortex consisted of necrotic tissue of the same appearance as described

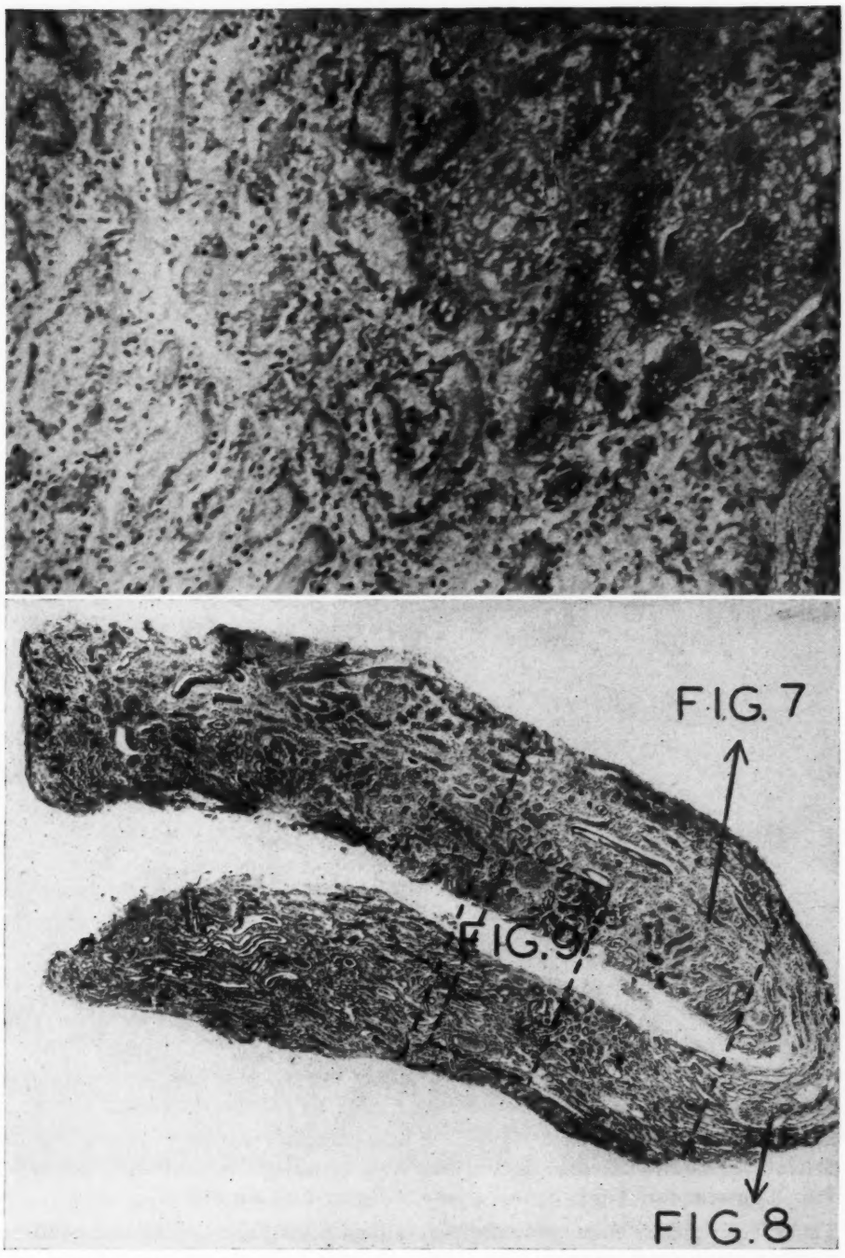

FIG. 5. Kidney biopsy showing almost completely necrotic, blood and leukocyte infiltrated cortex (acute bilateral cortical necrosis); × 145. (Case III, seventh day after onset of the disease.)

FIG. 6. Kidney biopsy on the eleventh day of the disease. The uppermost segment consists of almost completely necrotic cortex (as in Fig. 5); the intermediate zone is the intact juxtamedullary zone; the lower segment shows retained medulla with casts. (Case III.)

in the previous biopsy. Five or six glomeruli in this portion were almost completely necrotic. Hyaline casts were present in many of the damaged tubules. In the juxtamedullary zone there were two relatively well preserved glomeruli which showed only slightly diffuse hyalinization of the basement membranes. No necrosis or necrobiosis was seen in the medulla which contained considerable amounts of hyaline and many coarsely granulated hemoglobin-stained casts in the loops and the collecting ducts.

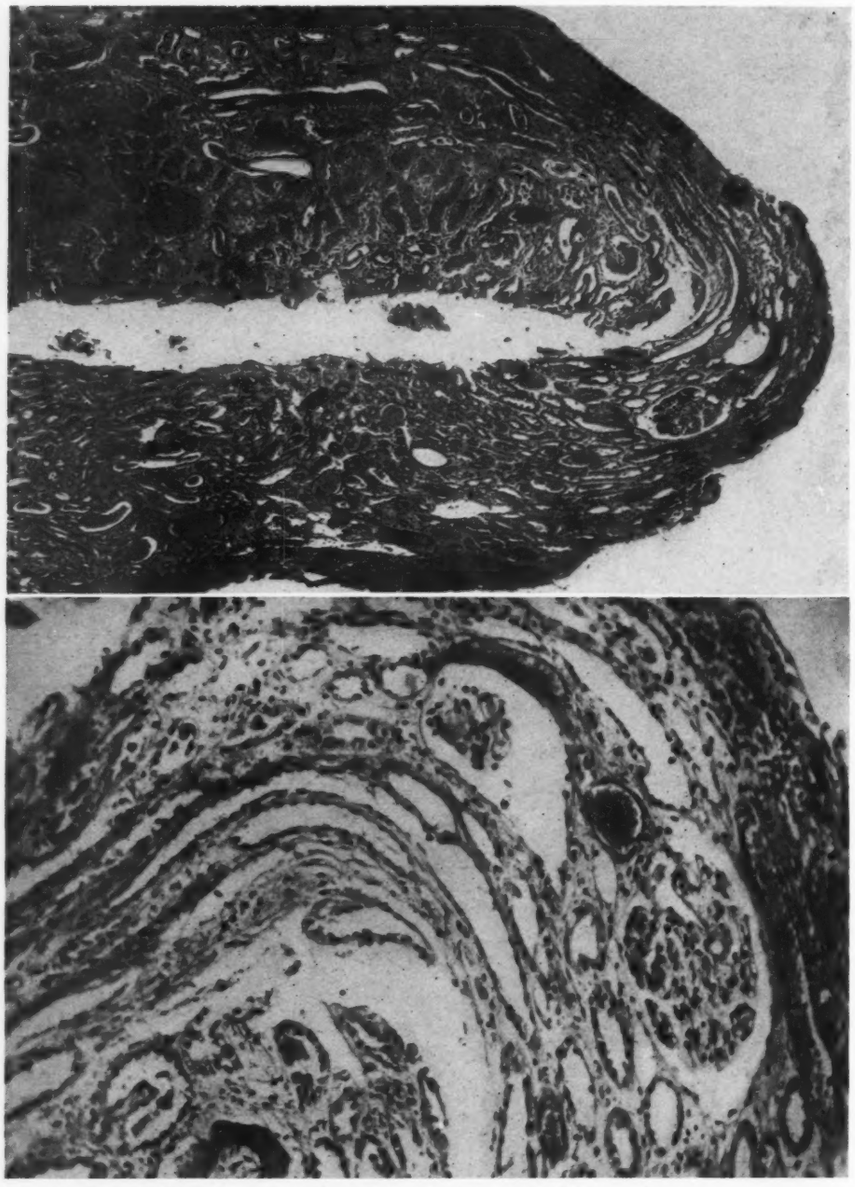

Fig. 7. Same kidney biopsy as that shown in Figure 6. (Case III.)

Fig. 8. Same kidney biopsy as that shown in Figs. 6 and 7; retained juxtamedullary zone with two intact glomeruli and a few hemoglobin-stained casts in distal tubuli; × 145. (Case III.)

In some places these lumina apparently contained pure blood. No inflammatory infiltration was noted in the medulla. No thromboses were found in the arteries in the two biopsies described above. The histologic diagnosis was: almost completely necrotic cortical tissue; medulla with casts of the type seen in tubulointerstitial nephritis.

The two kidney biopsies (kidney biopsy is always performed in the right kidney) and the clinical picture suggested either a large right-sided renal infarct with reflex anuria or large bilateral renal infarcts. In order to solve the question, renal arteriography according to Peirce's method was performed. The picture revealed normal renal arteries with normal, coarse ramifications; the suspicion of embolus or thrombosis in the renal arteries was thus invalidated.

The diagnosis of acute bilateral cortical necrosis would then be the most probable. This diagnosis was established with certainty

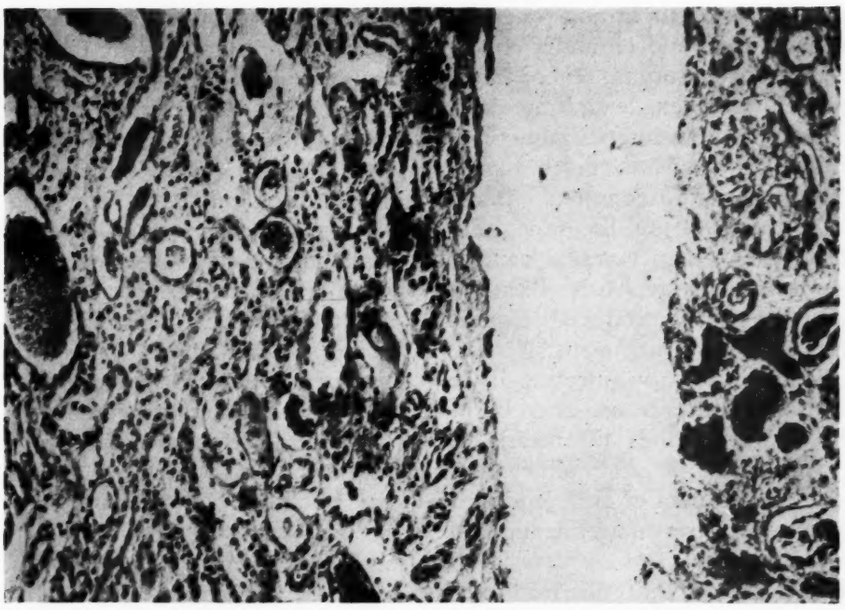

FIG. 9. Same kidney as Figures 6, 7 and 8. Left, retained medulla with hemoglobin-stained casts; right, almost completely necrotic cortex. × 145. (Case III.)

sixty-one days after the onset of the disease when tomograms were taken which showed diffuse calcinosis in the peripheral parts of the cortices of both kidneys.

Treatment and further course: Owing to persistent oliguria with marked impaired renal function (twenty-four hour endogenous creatinine clearance about 0.1 ml./minute) the serum urea level gradually rose to 432 mg. per 100 ml. and the serum creatinine to 24 mg. per 100 ml. As the serum potassium also showed a tendency to rise (Chart II), peritoneal dialysis was instituted on the fourteenth day of the disease (October 22). From the fourteenth to the thirtieth days of the disease the patient was given twelve dialysis treatments; 230 gm. of urea, 10 gm. of creatinine and 5.8 gm. potassium were removed in this manner. During the dialysis period the output of urine began to increase and, at the same time, there was a gradual rise in the twenty-four hour creatinine clearance. On the forty-fifth day it reached a level varying between 10 to 17 ml./minute; when the peritoneal dialysis was discontinued the serum urea had fallen to 250 mg. per 100 ml., the serum creatinine to 9 mg. per 100 ml. Later these values showed a further spontaneous fall to levels of 80 and 4 mg. per 100 ml., respectively.

On the seventy-fourth day of the disease the patient was discharged feeling very well. Three days after her discharge she was readmitted, this time to Surgical Department V, owing to ileus. As this could not be relieved by conservative treatment, surgery was performed and a segment of the small intestine was found to be twisted around a cord-shaped adhesion. Several other adhesions were found between the intestines. The operation was uneventful.

A follow-up nine months after the onset of the disease showed that the twenty-four hour creatinine clearance had risen to about 29 ml./minute; the serum urea was 59 and the serum creatinine was 2.5 mg. per 100 ml.

Summary and comments: Without preceding disease, a twenty-one year old non-pregnant woman suddenly suffered bilateral lumbar pain and complete anuria of five days' duration. On the basis of kidney biopsy the probable diagnosis was acute bilateral cortical necrosis, demonstrated two months after the onset of the disease by x-rays which showed calcinosis in the peripheral parts of the cortex of both kidneys. Kidney function during the first two weeks was practically nil. In the following two weeks peritoneal dialysis was performed and renal function gradually improved. Nine months after the onset of the disease function of the kidney was about one-quarter of normal and the patient was doing rather well.

Bilateral cortical necrosis, a rare disease, was first described by Juhel-Renoy in 1886.[14] It appears most frequently as a complication of pregnancy (bleeding and premature separation of the placenta) and after abortions.[7,26] The dis-

ease, however, may also occur in non-pregnant women and in males and children under conditions (severe hemorrhage, trauma, severe infection, dehydration, diarrhea, vomiting and burns) in which acute tubulo-interstitial nephritis occurs. Duff and Murray[7] have given a good survey of the literature and a complete clinical description. Pathogenesis of the disease is quite obscure but it is probably an extreme variant of acute tubulo-interstitial nephritis. Bilateral cortical necrosis has been produced experimentally in animals by various means: Byrom[4] produced the disease in rats by injecting large quantities of vasopressin; Penner and Bernheim[20] did the same in dogs by means of intraperitoneal injections of adrenaline, and both Navasquez[18] and Trueta et al.[26] produced the disease in rabbits by intravenous injections of staphylococcus toxin.

It is universally agreed that necrosis is of ischemic origin and that it is not due to multiple emboli (Duff and Murray[7]). Trueta et al.[26] and Sheehan and Moore[23] consider that the releasing mechanism must be a prolonged spasm in the interlobular arteries about 0.5 to 1 mm. from their origin from the arciform arteries; thus the juxtamedullary circulation would not be involved by the necrosis. Thromboses often occur in these arteries but they are considered secondary.

Several authors[5,9,17,22,24] have maintained that they have been able to diagnose the disorder clinically, after which the patient recovered. Clinically, the picture can hardly be distinguished from other forms of acute anuria; consequently it is not possible to establish a definite diagnosis without kidney biopsy. As far as we have been able to judge (and according to Trueta et al.) it seems that the diagnosis has hitherto been established with certainty only at autopsy.

With regard to differential diagnosis, acute pyelonephritis, urolithiasis with reflex anuria, acute glomerulonephritis and acute tubulo-interstitial nephritis must be considered. Signs characteristic of bilateral cortical necrosis include bilateral lumbar pain of sudden onset, oliguria-anuria, macroscopic hematuria, fever and absence of dysuria, pollakiuria and pain radiating to the region of the bladder. With regard to the other possibilities, cystoscopy, direct pyelography, renal arteriography and especially kidney biopsy will be decisive.

As the greater part of the glomeruli become necrotic, as in our case, it will undoubtedly prove to be characteristic that renal function is resumed slowly during treatment with dialysis and that it can be restored only to a limited extent. In spite of the small number of glomeruli present in the second kidney biopsy specimen it is interesting to note that the ratio between completely destroyed and preserved glomeruli correspond well to the level of renal function when treatment had been concluded. This was about 15 to 25 per cent of normal. (Chart II.) It would be reasonable to assume that in this respect bilateral cortical necrosis differs from acute tubulo-interstitial nephritis.

Bilateral cortical necrosis is a clinical counterpart to partial corticectomy performed on rabbits by Bing.[2] In Bing's laboratory, Sønder[25] has performed bilateral corticectomies in rabbits after renal hypertension had been established in advance by Goldblatt's method. Sønder showed that when partial corticectomy was carried out in early hypertensive animals with a duration of hypertension up to forty days, it was followed by a prompt and lasting fall in blood pressure. In our case hypertension did not develop during the acute phase of the disease and did not appear within 9 months after the onset of the disease.

SUMMARY

Three cases of acute oliguria-anuria are reported in which kidney biopsy was of great importance in proper interpretation.

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Studies in Serum Proteins*

Agammaglobulinemia in the Adult

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AGAMMAGLOBULINEMIA, the absence of both plasma and extravascular gamma globulin, has recently been found to be associated with unusually poor resistance to infection in certain patients.[1] The defect, which may be congenital or acquired, is more precisely described as a total lack of immunoglobulins since the antibody portion of the beta-2 globulins is absent as well as the gamma globulins, and the defect involves not only acquired antibodies but also such normal inherited antibodies as plasma hemagglutinins. The deficiency appears to be the direct result of an inability to synthesize immunoglobulins since in some such patients administered gamma globulin has been shown to have a normal or prolonged half-life.

Agammaglobulinemia is accompanied by a high mortality and a high incidence of repeated acute and later chronic infections of lung, liver and gastrointestinal tract. It is therefore not surprising that the majority of patients described to date have been children, carefully studied by Janeway and his associates.[2] These cases were believed to represent a congenital form of the disease with sex-linked inheritance, since all affected children were males. However, a rapidly increasing number of reports of agammaglobulinemia in the adult are appearing, representing both the congenital and acquired forms of the syndrome.[3–10] Agammaglobulinemic females are included among these cases. One patient, who will be discussed in the present report, was briefly mentioned some years ago.[11]

The diagnosis of agammaglobulinemia can be easily made because the clinical manifestations are highly suggestive and, once the possibility has been considered, simple laboratory tests quickly establish or refute the diagnosis. The disease provides an excellent example of the value of the pathophysiologic approach since its many clinical and laboratory characteristics may be deduced from a knowledge of the basic defect.

Agammaglobulinemia should be suspected when there is: (1) A history indicating grossly inadequate resistance to infection. Such patients usually give a history of repeated acute episodes of pneumonia, otitis media, meningitis, hepatitis and enterocolitis. Bronchiectasis, chronic hepatitis or sprue-like syndromes may be fully developed when the patient is first seen. (2) Failure to develop clinical immunity or expected laboratory evidence of antibody production after adequate antigenic stimulus. There may be a definite history of two attacks of a disease which normally confers permanent immunity, such as rubella or mumps. Before, during and after an infection with a known specific organism no significant titer of antibody is demonstrable in the serum. Furthermore, no antibody response follows challenge with known potent antigens. Skin tests of the tuberculin type remain negative and the Schick and Dick tests are persistently positive. (3) An unexpectedly normal result with a laboratory test which depends upon abnormalities in serum gamma globulin. The thymol turbidity, cephalin-cholesterol flocculation and colloidal gold flocculation tests are normal although the patient's status suggests they should be abnormal. The Kunkel "gamma globulin" is low when normal or high values would be expected, and the Howe A/G ratio is

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high when normal or low values would be expected. (4) An absence of normally inherited plasma isohemagglutinins.

Diagnosis is established by demonstrating the absence of serum gamma globulin by specific chemical or electrophoretic technics.

METHODS AND SUBJECTS

Clinical studies in Cases III and IV were carried out at the Michael Reese Hospital, in the former instance with the cooperation of Dr. Boris B. Rubenstein, and in the latter with the cooperation of Dr. Norman F. Boas and the late Dr. Henry S. Guterman.

Serum protein patterns were obtained by the chemical micromethod of Wolfson and Cohn,[12] by filter paper electrophoresis employing apparatus and technics developed in this laboratory,[13] and by free electrophoresis in the Aminco-Stern (Case IV) or Perkin-Elmer (Case II) instrument.* Free electrophoresis was conducted in barbital buffer, pH 8.6, ionic strength 0.1. For paper electrophoresis the buffer had the same pH but the ionic strength was 0.05, and 10 per cent of ethanol (v/v) was added to inhibit mold and adsorption. Electropapergrams were dried in an oven at 100°C., fixed in bichloride of mercury and simultaneously stained with bromphenol blue. Excess bromphenol blue was then removed by exhaustive washing in 0.5 per cent aqueous acetic acid, the paper dried in an oven and the indicator dye converted to the blue form by exposure to ammonia. The electropapergram was then scanned either with a Gamma I scanning photometer or with the Wolfson-Skinner strip-scanning adapter for the Beckman DU spectrophotometer. The resulting curves were measured planimetrically in the usual manner. Other chemical determinations employed routine current laboratory technics.

CASE REPORTS

The typical history of an agammaglobulinemic patient is a stormy one and is well illustrated by Case I, which will therefore be presented in some detail.

CASE I. The history prior to study in this Unit is best summarized chronologically as follows: Age one to three years, apparently normal; four years, bilateral purulent otitis media, many exacerbations in subsequent years; five years, scarlet fever; seven years, varicella, rubella, pertussis and acute mastoiditis; ten years, suppurative cervical adenitis, poliomyelitis; eleven years, suppurative cervical adenitis, infectious hepatitis, lobar pneumonia; twelve years, rubella, lobar pneumonia; thirteen years, lobar pneumonia, suppurative cervical and inguinal adenitis, diagnosis of bronchiectasis established; fourteen to seventeen years, many episodes of pneumonia; seventeen years, operation for chronic sinusitis; eighteen years, two attacks of lobar pneumonia, lobectomy for severe symptomatic bronchectasis; nineteen years, four attacks of lobar pneumonia, purulent meningitis, diagnosis of hepatic cirrhosis established; twenty years, two attacks of lobar pneumonia. Throughout these twenty years he also had a multitude of minor infections and ill defined febrile episodes. The diagnosis of agammaglobulinemia was made in September, 1953, when the patient entered the City of Detroit Receiving Hospital because of lobar pneumonia.

TABLE II

SERUM PROTEINS IN AGAMMAGLOBULINEMIA, ILLUSTRATING THE CHARACTERISTICALLY HIGH HOWE A/G RATIOS

	True A/G Ratio	Howe A/G Ratio
Agammaglobulinemia		
Case I	3.3	13.4
Case II	1.6	3.5
Case III	3.1	10.3
Case IV	1.3	4.8
Normal adult		
Average value	1.2	2.3

The patient's parents, sister and four brothers were living and well. One brother had died at the age of one, apparently of pneumonia. Physical examination disclosed a chronically ill and somewhat underdeveloped white male. He was 67 inches tall and weighed 118 pounds. He had chronic bilateral otitis media, extensive bronchiectasis of the right lower lobe, hepatosplenomegaly and generalized shotty lymphadenopathy.

Table I summarizes the pertinent laboratory findings. Needle biopsy of the liver disclosed early portal cirrhosis without lipidosis. A lymph

* For the free electrophoresis analyses we are indebted, respectively, to Dr. Ivan F. Duff of University Hospital, Ann Arbor, Mich., and to Miss Miriam Reiner of Mount Sinai Hospital, New York, N. Y.

node biopsy revealed normal node architecture with mild reactive reticulum cell hyperplasia. A bone marrow study showed no significant abnormalities. Chemical fractionation of the serum proteins and paper electrophoretic studies disclosed a total absence of gamma globulin. (Fig. 1.)

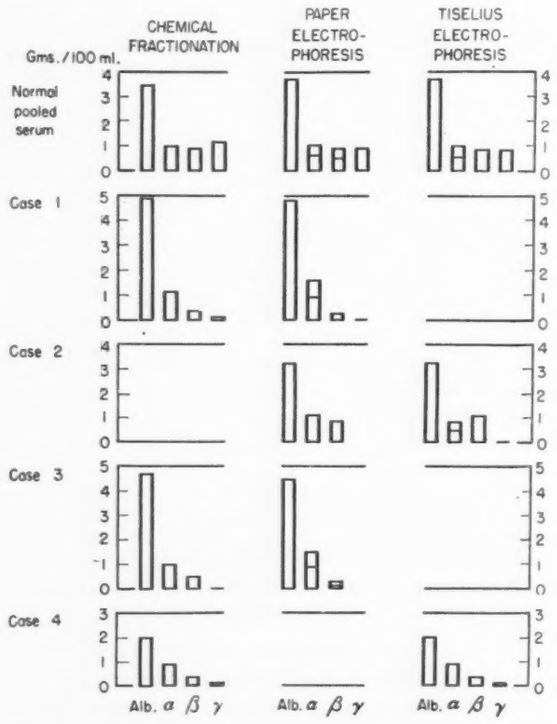

FIG. 1. Agammaglobulinemia; serum protein fractionation studies.

CASES II, III AND IV. These three adult males with proved agammaglobulinemia ranged in age from twenty-six to thirty-three years. All had had frequent infections since early childhood, with bronchopulmonary involvement predominating. One had definite bronchiectasis. Attempts to detect an antibody response to administered antigens were uniformly unsuccessful. Howe A/G ratios were all unusually high. Chemical fractionation of the serum proteins by the method of Wolfson and Cohn, by classical Tiselius electrophoresis, or by paper electrophoresis disclosed an absence of circulating gamma globulin. (Table II, Fig. 1.)

RESULTS

Protein Fractionation Studies in Patients with Agammaglobulinemia. Figure 1 shows the complete absence of gamma globulin from the sera of all these patients. The beta-2 globulin concentration, although somewhat difficult to estimate by paper electrophoresis, clearly was low in Cases I and III. Other fractions show only those abnormalities anticipated from the patients' clinical status. High serum alpha globulin would be expected because of the presence of chronic suppuration in Cases I, III and IV and because of recent acute infection in Case II. Hypoalbuminemia in Case IV was found shortly before the patient died of chronic suppurative pulmonary disease. Apparently, the primary changes in serum proteins involve only the beta-2 and gamma globulin fractions, a finding consistent

TABLE I
PERTINENT LABORATORY FINDINGS IN CASE I

Serum total protein	6.55 gm. %	Kunkel gamma globulin test	1 unit
Howe serum albumin	6.10 gm. %	45-minute bromsulfalein retention	20 %
Howe serum globulin	0.45 gm. %	Serum cholesterol	250 mg. %
Howe "A/G ratio"	13.4	Blood hemoglobin	14 gm. %
Serum bilirubin	0.4 mg. %	Blood urea nitrogen	14 mg. %
Urine bilirubin	Negative	Congo Red test	Negative
Urine urobilinogen	Negative	Blood type	A_1
Schick test	Positive	Anti-b and anti-a_2 plasma isohemagglutinins	Absent
Tuberculin test	Negative		
Cephalin flocculation test	Negative		

	Total Leukocytes	Granulocytes	Lymphocytes + Monocytes
Normal range	5,000–10,000	3,000–5,800	1,785–3,500
Patient, afebrile	9,100	4,368	4,550
Patient, febrile	19,800	16,434	3,168

with their postulated special function and their site of synthesis.

Howe Fractionation Values in Agammaglobulinemic Patients. When sodium sulfate is added to serum in an amount sufficient to give a final concentration of 21 per cent, a portion of the serum proteins precipitates. In this original technic of Howe the protein precipitated is designated "globulin," while that still in solution is termed "albumin." However, the "albumin" of the Howe method actually includes both the true albumin and part of the alpha globulin as estimated by the Wolfson-Cohn chemical fractionation procedure or by free or paper electrophoresis. The "globulin" of the Howe method includes largely the beta globulin and the gamma globulin of modern methods.

From these considerations it is apparent that the "albumin"/"globulin" (A/G) ratio of the Howe method approximates

$$\frac{\text{albumin plus alpha globulin}}{\text{beta globulin plus gamma globulin}}$$

as estimated by the Wolfson-Cohn chemical fractionation or by electrophoresis. In agammaglobulinemia the denominator is small because of the absence of the gamma globulin component and the reduced beta-2 globulin devoid of immunoproteins. In relatively healthy patients with this disorder the numerator will have its normal value; but even if albumin is reduced, as in Case IV, the rise in alpha globulin concentration which is usually associated with a fall in albumin will tend to minimize any decrease in the numerator. The patient with agammaglobulinemia therefore has a high Howe "albumin"/"globulin" ratio because the numerator is relatively normal while the denominator is greatly reduced. In three of the cases herein reported the routine laboratories processing the Howe fractionation values suspected laboratory error because the A/G ratios were so high.

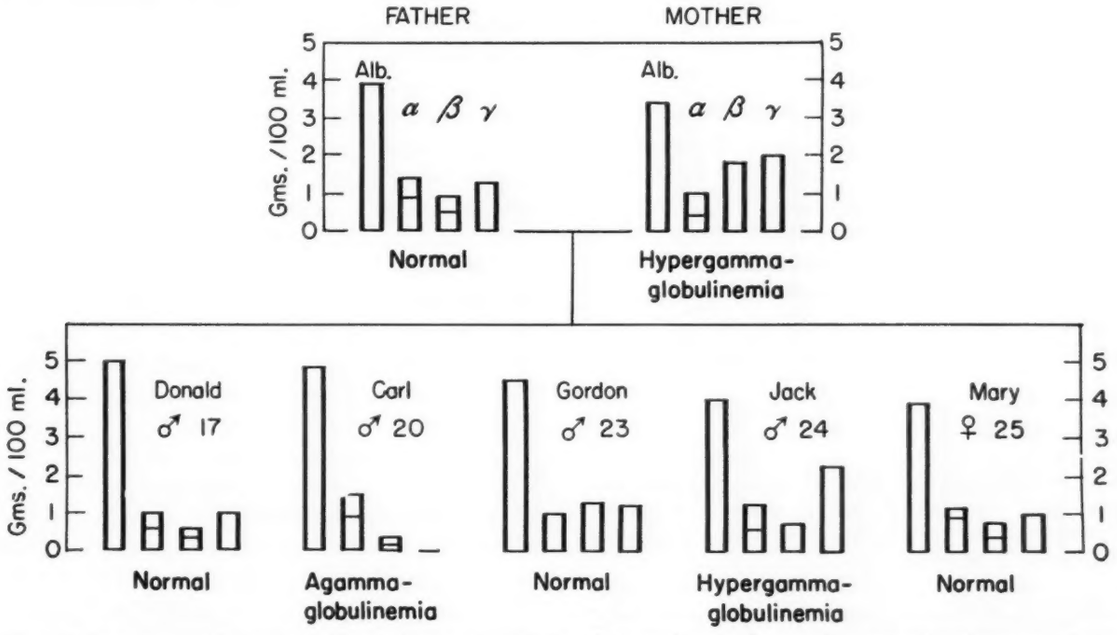

FIG. 2. Serum protein fractionation studies on the family of the patient in Case I, demonstrating hypergammaglobulinemia in two members.

Protein Fractionation Studies in Unaffected Relatives of Patients with Agammaglobulinemia. Serum proteins were examined in unaffected relatives of two of our patients (Cases I and III), and in a number of the patients studied by Janeway and associates.[14] Abnormal patterns have been found only in the family of our Case I. His mother and one of his brothers both showed marked hypergammaglobulinemia and hyperbeta-2-globulinemia, which could not be explained clinically. (Fig. 2.)

Other Findings in Agammaglobulinemic Patients Which Suggest Absent Circulating Gamma Globulin or Antibody. Naturally occurring plasma isohemagglutinins were absent in Case I and in patients studied by Bruton and Janeway. Since

these substances are known to be beta-2 globulins, their absence correlates well with the electrophoretic finding of a low beta-2 globulin value. All reported patients have been blood types A or O but, because of absent isohemagglutinins, all are presumably universal recipients.

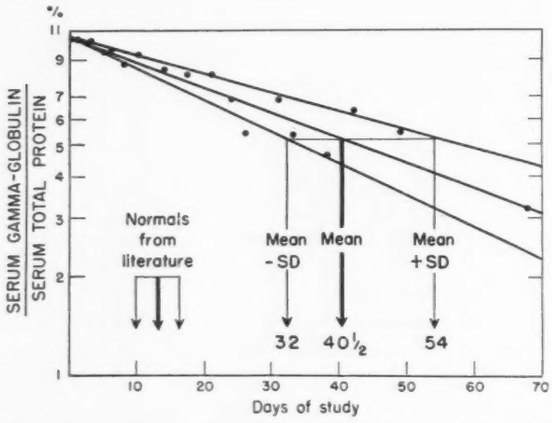

FIG. 3. Case I. Half-life of administered human gamma globulin; normal values are based on the half-life of I-131 labeled gamma globulin. Recent evidence indicates that such values are probably low. Therefore, the half-life of the unlabeled gamma globulin administered to this patient is probably not abnormally prolonged.

Another anticipated observation is the failure of intercurrent disease, particularly liver disease, to produce abnormal protein flocculation tests, because all appear to require some elevation or abnormality of gamma globulin before they become positive. This is well illustrated in Case I. (Table I.) Patients with agammaglobulinemia do have erythrocyte sedimentation rates consistent with their state of health or illness because fibrinogen, the chief plasma protein determinant of the sedimentation rate, shows its usual increase in response to illness or injury.

Defective Response to Antigenic Challenge. Agammaglobulinemic patients are incapable of responding to antigen by producing specific antibodies, whether the antigenic stimulus is a naturally occurring disease or a purified antigen. The common skin tests do not change after appropriate stimulation with antigens. Three patients of this series (Cases I, II and III) produced no circulating antibody after repeated administration of typhoid vaccine. The Schick tests were positive. The tuberculin test was negative in Case I. In the cases reported by Bruton and Janeway there was no antibody response to administered pneumococcal polysaccharide or typhoid vaccine. In one case no complement-fixing antibodies for mumps could be demonstrated in the serum twenty-two days after a typical attack. Schick tests were noted to remain positive in spite of repeated administration of diphtheria toxoid. This phenomenon is responsible for a characteristic clinical feature of the syndrome, namely, the occurrence of more than one attack of a disease which normally confers lasting immunity, such as mumps, pertussis and measles.

The response to vaccination is unanticipated and forms almost the only finding in agammaglobulinemic patients which is at all inconsistent with expectation. Janeway et al.[2] have indicated that a primary "take" may be obtained and that if such a patient is revaccinated an accelerated reaction indicative of partial immunity may be seen. This, of course may represent a type of adaptation not involving immunoglobulin formation and, if so, suggests the presence of previously unrecognized factors in resistance to infectious disease.

Blood Lymphocyte Counts and Lymph Node Histology. Experimental studies have suggested that fixed tissue lymphocytes either may become liberated as blood lymphocytes or, while still located in the lymphoid tissue, may undergo cytolysis and give rise to blood antibodies by shedding their surface protein film. It has been suggested that the relative rates of these two processes is dependent upon adrenal glycocorticoids, higher levels favoring the cytolytic process.[15]

In Cases II, III and IV peripheral blood lymphopenia was persistently present, the absolute lymphocyte counts ranging from 798 to 1,117 per cu. mm. The absence of associated eosinopenia or neutrophilic leukocytosis clearly showed that an increased level of adrenal corticoids was not the cause of this lymphopenia. Its probable origin was indicated by the changes found in the lymph nodes of two of these patients. In both, the nodes appeared markedly hypoplastic and severely deficient in tissue lymphocytes (lymphoblasts). By contrast, the remaining apparently intact reticular framework was unusually prominent. Janeway and Bruton have examined nodes, selected from a number of regions, and have found either a similar deficiency of tissue lymphocytes or an absence of germinal centers.[16] Either finding suggests diminished lymphopoiesis, since the prominence of the germinal center is believed to be an index of the rate of lymphocyte formation. Thus in these patients it

would appear logical to explain the absence of gamma globulin, the blood lymphopenia and the quantitative lack of tissue lymphocytes seen at biopsy or implied by the absence of germinal centers as due to greatly reduced lymphopoietic activity. Because this view fails to explain why there should be a relative deficiency of blood lymphocytes and a complete absence of blood immunoglobulins, it would seem that defective release of antibody from templates must also be postulated.

In Case I, however, the peripheral blood lymphocyte count was in the high normal range when the patient was afebrile, and during infections it changed in the normal manner. Several lymph nodes and diffuse lymphoid tissue from the Waldeyer ring area of the nasopharynx were found to be normal except for some sinusoid dilatation and reticulum cell hyperplasia in these dilated sinusoids.

The agammaglobulinemia of Case I was quite as complete as that of the other patients in spite of normal-appearing lymphoid tissue. Since no evidence of slowed lymphopoiesis could be found, this patient in contrast to the others described, may have some qualitative disturbance in the protein-synthesizing mechanism of his tissue lymphocytes. This interpretation is supported by the isolated hypergammaglobulinemia observed in persons whose relationship makes it plausible to assume that they are heterozygous carriers of a recessive gene which produces agammaglobulinemia without lymphopenia in a homozygote.

Absence of Effect of ACTH and Other Medications on Serum Proteins and Peripheral Blood Counts. ACTH was administered to one patient with the lymphopenic type (Case II) and one patient with the non-lymphopenic type (Case I) of agammaglobulinemia. One patient with each of the types of agammaglobulinemia responded to test doses of ACTH with normally intense eosinopenia and lymphopenia. Following intensive courses of treatment with ACTH gel for seven to eight days, no detectable amounts of gamma globulin were noted. Neither relative corticoid deficiency nor excess seems to provoke or relieve agammaglobulinemia of either type.

Because hypogammaglobulinemia has occurred in experimentally induced pyridoxine deficiency in animals, large doses of pyridoxine (100 mg./day), with and without whole vitamin B complex, were administered for prolonged periods to two patients (Cases I and II) without effect. Large amounts of desoxyribonucleic acid were fed to one patient because of the work of Dustin[17] who found that it caused thymic and lymphatic hyperplasia. No significant change was noted.

Rate of Disappearance of Administered Human Gamma Globulin in Agammaglobulinemia. The half-life of administered gamma globulin in several children with agammaglobulinemia was reported to range from twenty to thirty days,[14] values slightly longer than normally found in children. Figure 3 demonstrates the apparently prolonged half-life of homologous gamma globulin in Case I. In Case III the rate of disappearance of administered gamma globulin was found to be within the normal range for adults. These observations exclude rapid catabolism of gamma globulin as an explanation for this syndrome. They also suggest that as plasma-globulin levels fall the relative amount utilized per unit time decreases.

DISCUSSION

Physiologic Basis of Therapy in Agammaglobulinemia. Normally about 13 per cent of the total serum protein consists of gamma globulins, chiefly immunoproteins, together with a considerable quantity of "non-specific" gamma globulin of as yet unknown significance. Certain antibodies, including blood group isohemagglutinins, typhoid "O" agglutinins and true Wassermann reagin are also found in the beta-2 globulin fraction.[18] The normal adult has approximately 25 gm. of circulating gamma globulin in dynamic equilibrium with an equal quantity of extravascular gamma globulin.[19] The serum level of gamma globulin appears to be closely related to adaptive processes. It is relatively high at birth, presumably due to transplacental transmission of antibodies, falls for several months, and thereafter rises slowly as the individual comes into contact with immunizing diseases. Adult levels are not reached for over two years.

The half-life of gamma globulin, as determined by the administration of homologous I-131 labeled gamma globulin,* is 13.1 $\pm$ 2.8 days in adults, and somewhat longer in children, 20.3 $\pm$ 4.1 days.[20] The normal adult, therefore, apparently catabolizes about one-thirteenth of

* The validity of values obtained by this method has recently been questioned. Armstrong et al. have reported turnover times of nineteen to twenty-three days using S^{35}-labeled yeast (*J. Lab. & Clin. Med.*, 44: 762, 1954).

his 50 gm. of gamma globulin, approximately 3.8 gm., each day.

Replacement therapy with human gamma globulin has been reported effective in controlling the principal manifestations of this syndrome. Affected children have been maintained free of sepsis on weekly injections of gamma globulin and prophylactic penicillin.[1,14] It is apparently neither necessary nor practical to achieve normal blood levels of gamma globulin to prevent infection. Gitlin has noted that levels of only 100 to 150 mg. per 100 ml. are effective.[14] This is fortunate since it may be calculated that an adult would require about 25 cc. of the commercial 15 per cent gamma globulin solution per day for complete replacement. The material cannot be administered intravenously because of severe hypotensive reactions, and intramuscular injections of over 20 ml. are prone to cause chills, fever, myalgia and faintness. Since the virus of homologous serum jaundice is not associated with the gamma globulin fraction, there is little danger of serum hepatitis, even with prolonged administration.

Site of Origin of Immunoglobulins. The existence of a disorder in which immunoglobulins are absent and other serum proteins are unaffected indicates a special site and mechanism for synthesis of immunoglobulin. The lymph nodes and spleen are known to be important sources of antibodies but the specific cell type which forms antibodies has not been established with certainty. Despite much investigation, various workers favor reticuloendothelial cells, immature tissue lymphocytes, plasma cells or several of these as the synthesizing organ.[21,22] Simultaneous absence of immunoglobulins and evidence of slowed lymphopoiesis in one group of patients favors the immature tissue lymphocyte; however, the existence of a non-lymphopenic type of agammaglobulinemia shows that all factors are not yet known.

Differential Diagnosis of Hypogammaglobulinemia. A subnormal level of plasma gamma globulin results from a disproportion between its rate of synthesis and the rate at which it is utilized. Once the rate of synthesis becomes less than the rate of utilization, the level would fall to zero unless the decrease in concentration also brought about a diminished rate of utilization. The prolonged half-life of injected gamma globulin in agammaglobulinemic subjects suggests that utilization is slower at low levels.

A subnormal rate of gamma globulin synthesis may occur when normal lymphoid tissue receives an insufficient supply of precursors or when a normal precursor supply is delivered to hypofunctioning lymphoid tissue. Knowledge of the precursors of gamma globulin is relatively incomplete. Within wide limits, synthesis is not critically dependent upon protein intake in normal subjects. In certain rare patients believed to have a selective type of hepatic dysfunction,[23] hypogammaglobulinemia even at high levels of protein intake has been described. Apparently, the liver makes some unknown metabolite essential for subsequent formation of gamma globulin by lymphoid tissue. This essential metabolite would appear always to be in limited supply, since hypogammaglobulinemia may occur when an abnormal protein is produced at a rapid rate (v. seq.), even though the lymphoid tissue is histologically normal. In suitably designed animal experiments, hypogammaglobulinemia may be induced by deficiency of pantothenic acid or pyridoxine or by the pyridoxine antagonist, desoxypyridoxine.[24] The required degree of deficiency is severe and clinical hypogammaglobulinemia has never been shown to result from a deficiency in either of these two vitamins, which are essential in coenzymes of protein synthetic processes.

Hypogammaglobulinemia which results from a deficient supply of precursors is never complete; and since minimal levels of functionally active immunoglobulins apparently suffice for normal resistance, unusual susceptibility to infection is not prominent in the disorders just cited. The major symptoms are usually edema and ascites, the result of an associated diminution in the synthesis of plasma albumin. The available but still scanty data are consistent with the expected normal or prolonged half-life of injected gamma globulin or albumin.

Hypogammaglobulinemia is not uncommonly seen in multiple myeloma with a beta globulin or M-component abnormality, and may well be due to diversion of gamma globulin precursors for the synthesis of the abnormal component. The electrophoretic pattern of an unusual case of apparent agammaglobulinemia associated with an M-component myeloma is presented in Figure 4. The patient had a history of many bouts of sepsis, particularly pneumonia, since the onset of the disease. He failed to develop antibodies in response to typhoid vaccination, and the tuberculin and histoplasmin skin tests were negative. However,

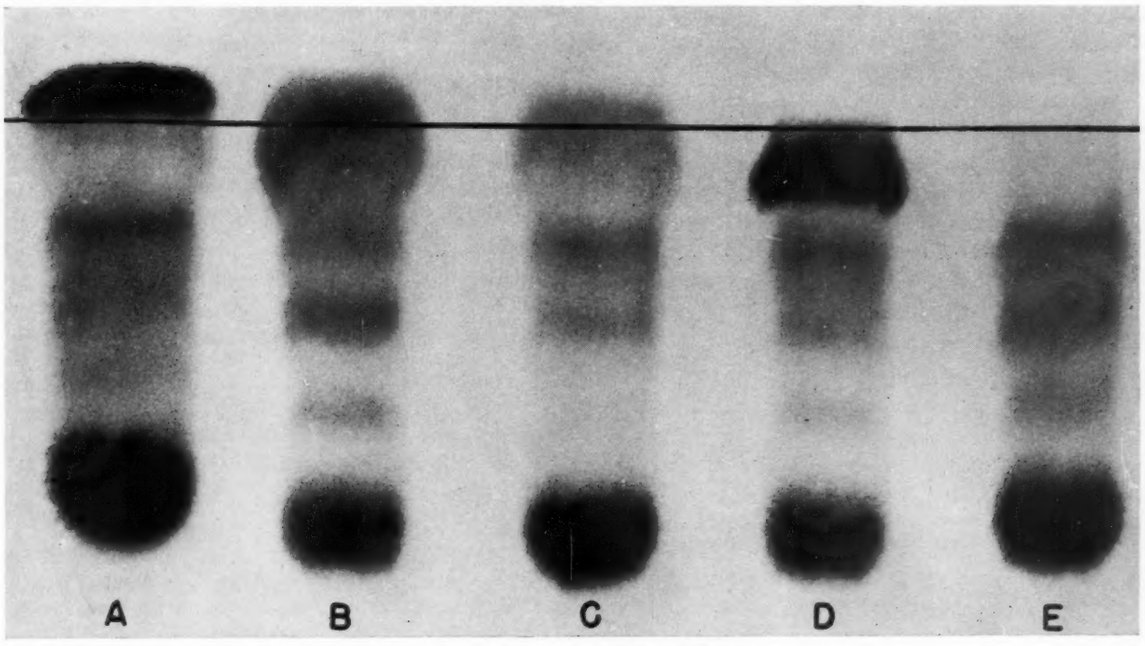

FIG. 4. Case I. Electropapergrams of 5 sera, illustrating gamma globulin abnormalities. A, gamma myeloma, the abnormal gamma globulin fraction consisting almost entirely of cryoglobulin; B, hypergammaglobulinemia in a case of disseminated lupus erythematosus; C, normal serum; D, M-component myeloma with agammaglobulinemia, the abnormal globulin consisting largely of pyroglobulin; E, congenital agammaglobulinemia. Transverse line indicates point of application of serum.

isohemagglutinins were present in the serum, indicating that the immunoglobulin-synthesizing defect was not inherited or complete.

Given an adequate supply of essential precursors, deficient production of gamma globulin may still occur if the lymphoid tissues function inadequately. The total mass of the synthesizing tissue may be greatly reduced by cancerous replacement, by radiation damage or by certain radiomimetic chemicals, notably benzol and nitrogen mustards. A quantitative defect in lymphoid structures may also be congenital, as is probably true of Cases II, III and IV in this report. In addition, the data in this paper suggest that more subtle qualitative hypofunction of lymphoid structures may occur (Case I).

Hypofunction of the lymphoid structures concerned in gamma globulin synthesis is not ordinarily associated with a similar disturbance in albumin formation, so that ascites and edema are not an integral part of the symptomatology. It may, however, lead to complete agammaglobulinemia with its characteristic clinical picture. In these disorders, the half-life of injected gamma globulin is normal or prolonged and, if agammaglobulinemia is present, complete failure of synthesis is shown by the absence of an antibody response to antigenic challenge.

Abnormally rapid loss of gamma globulin from the plasma is the most common cause of clinical hypogammaglobulinemia. In the nephrotic syndrome there is excessively rapid transcapillary loss of gamma globulin, with a parallel loss of albumin, in the urine. Hypogammaglobulinemia as well as hypoalbuminemia has also been described in rare cases of familial idiopathic dysproteinemia,[25] an interesting disorder resembling the nephrotic syndrome but without renal abnormalities.

Other theoretic causes for an increased rate of gamma globulin removal include fixation in antigen-antibody reactions and an increased rate of protein catabolism. The fall in plasma gamma globulin often seen in Cushing's syndrome and reproducible in normal adults with corticotropin may result from an increased rate of protein catabolism, overshadowing a less marked increase in the rate of gamma globulin synthesis.

SUMMARY

Agammaglobulinemia is a syndrome which may be due to congenital or acquired factors. The clinical manifestations are readily explained by failure of immunoglobulin synthesis due to a defect in the synthesizing tissues. Such patients have a history of grossly inadequate resistance

to infectious disease, and fail to produce antibodies in response to natural or artificial antigenic challenge.

Four cases of adult agammaglobulinemia are described. All patients were men. In three cases agammaglobulinemia was associated with a quantitative deficiency in tissue and peripheral blood lymphocytes, and relatives were apparently unaffected. One patient had no apparent lymphocyte abnormalities, and relatives of both sexes manifested hypergammaglobulinemia.

The disorder is readily diagnosed by serum protein electrophoresis or chemical fractionation studies and is believed to be amenable to specific replacement therapy with human gamma globulin.

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Review

Studies of Ulcerative Colitis*

III. The Nature of the Psychologic Processes

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In previous papers I have discussed the various psychosomatic hypotheses concerning ulcerative colitis in terms of their consistency with data available as to the nature of the somatic processes.[19,20] It was concluded that the anatomic and functional locus of the disease is the lining surfaces (mucosa and submucosa) of the colon and ileum, and that the nature of the process more closely resembles a reaction to a microscopic or molecular-sized noxious agent than a bolus-sized agent. Evidence was presented to show that the primary reaction is at this level of tissue organization, with hyperemia, edema, exudation and secretion as prominent components, while the behavior of the colon as a whole, as reflected in the character of the bowel movements, diarrhea or constipation, is dependent upon the location and severity of the local reaction. When the surface reaction is restricted to rectum or rectosigmoid, constipation is the rule, whereas when the process involves proximal bowel or extensive segments of bowel, diarrhea is usual. Such relationships are most readily detected at the inception of the disease and, once bowel has been damaged, other factors influence symptomatology in unpredictable ways. In light of these facts it was concluded that none of the psychosomatic processes so far advanced properly identify the somatic processes and therefore require re-evaluation.

In this paper I propose to examine the available data concerning psychologic processes in ulcerative colitis, summarizing the literature as well as my own observations. In doing so I am influenced by the fact that few physicians have had or ever will have the opportunity to obtain this kind of information in more than a few patients and therefore there is a need to bring together in one place all the facts as well as some indication of the number and variety of patients upon which such facts are based. The frame of reference employed is a broad one. In studying psychologic processes attention is directed to one aspect of the total functioning of the human being, that which can be examined by psychologic means and expressed in psychologic terms. We deal with the observable phenomena of intrapsychic and interpersonal processes, including ontogenetic aspects. This material is then analyzed for any consistent patterns in this group of patients as a whole, as well as in relation to exacerbations and remissions of the pathologic processes in the colon. No assumption is made that such correlations have etiologic significance. We are at this time attempting only to establish the existence and nature of conditions which may be contributory or even necessary yet may not be sufficient in themselves for the development of ulcerative colitis. We do not concern ourselves here with the problem of psychogenesis in the sense of psychologic processes *causing* ulcerative colitis. This kind of a study may be compared to the epidemiologic approach to malaria, in which information about geography, climate, breeding conditions of mosquitoes, the life cycle of the mosquito, the conditions necessary for survival of the malarial parasite, the conditions necessary for the transmission of the parasite from vector to human host and back again, the factors of host resistance, and many others all combine to define the conditions necessary and sufficient for the development of the disease malaria. The identification and elucidation of any one condition represents an important advance in the understanding of the disease

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but does not "explain" pathogenesis or establish etiology. Similarly, psychologic study of patients with ulcerative colitis represents but one step in the clarification of conditions necessary, but not necessarily sufficient, for the development of the disease. Whether or not such an approach will prove fruitful in the study of any particular disease entity cannot be established until the study has been carried out.[23,24]

The matter of significance must also be discussed here. The fact that certain phenomena are observed consistently, or even commonly, in a group of patients justifies their further study. Critics of the psychologic approach often dismiss as of no significance the observation that some psychologic event commonly precedes the development of an organic process by pointing out that many people experience the same kind of psychologic event without developing the disease, and therefore the two cannot be related. This, however, would be the same as arguing that the typhoid bacillus cannot be a significant factor in typhoid fever because many people who are exposed to the organism do not develop the disease. It ignores the vulnerability of the individual. Pettenkoffer's dramatic attempt to refute the significance of vibrio cholera by publically ingesting a culture of living organisms is a case in point.

And finally it is necessary to stress the importance of method. It is not possible to evaluate the importance of psychologic factors unless the material is examined by methods appropriate for that kind of evaluation.

MATERIAL AND METHODS

This paper is based upon examination of forty-four published reports of psychologic data in more than 700 patients with ulcerative colitis, plus observations in thirty-nine patients of my own, not all of whom were studied with the same thoroughness. Many of these reports represent pooled impressions of a large number of patients,[48a,55,56] while others represent single case reports. Of this large published material there are only forty-one reasonably detailed protocols which permit the reviewer opportunity for examination of more primary data. Some papers do not mention the number of cases upon which the conclusions are based. And in many it is very difficult to know which interpretations are derived from the writer's own observations and which are reflections of earlier writings.

No attempt will be made to review or summarize each paper. Instead I have selected for critical evaluation certain categories of psychologic processes and have examined the literature as well as my own data for material bearing on the phenomena under consideration. In so doing it was sometimes necessary to use and interpret data from the publications of other writers in ways which they did not emphasize.

ANAMNESTIC AND PSYCHOANALYTIC STUDIES

Anamneses vary from relatively superficial reports by observers with little psychologic training to histories obtained by psychoanalytically trained physicians. While quite a few patients with ulcerative colitis have been analyzed and considerable material is available from such sources, reasonably detailed protocols of psychoanalyses are still few.[13,14,25,38,51,52,66] The psychoanalytic method, however, involving as it does long and detailed study of the patient, clearly establishes that the major psychodynamic trends long antedate the development of clinically manifest ulcerative colitis. The often repeated assertion that the psychologic characteristics of these patients are the consequence of the severe and debilitating disease finds no support when patients are studied for years, including long periods of complete remission.

Personality Structure

Under this heading are grouped the more or less characteristic behavioral patterns of an individual, the person's peculiar mode of dealing with psychic tension.[3]

A high proportion of patients are described as manifesting obsessive-compulsive character traits, including neatness, orderliness, punctuality, conscientiousness, indecision, obstinacy and conformity. Along with these are often noted a guarding of affectivity, overintellectualization, rigid attitudes toward morality and standards of behavior, meticulousness of speech, avoidance of "dirty" language, defective sense of humor, obsessive worrying and timidity. Alexander[1] in particular has stressed the prominence of the so-called anal characteristics. (See references 2, 5–8, 10, 11, 13, 17, 25, 31, 32, 34, 38, 43, 47, 48*a*, 50, 51, 55–59, 64, 66, 68–71, 78, 80.) The deviations from this pattern are of interest. A few patients are conspicuously sloppy, disorganized, dirty and unkempt—some of these are psychotic.[25,41,42,80] During the active disease and during analysis the patient may betray an extraordinary preoccupation with feces which

contrasts with his usual fastidiousness.[25,45,46,64,66] Some patients are petulant, querulous, demanding and provocative, but well directed aggressive action and clear-cut expressions of anger are uncommon. (See references 7, 25, 31, 34, 35, 51, 55, 57–59, 69, 80.) Many writers have been impressed with the extreme sensitivity of these patients, their almost uncanny perception of hostility or rejecting attitudes in others. They are easily hurt, constantly alert to the attitudes and behavior of others toward them, tend to brood and withdraw. Much activity is devoted to warding off or avoiding rebuffs, including placating attitudes, submission, politeness, attempt to please and conform, seductive behavior. Others use denial, remaining proud, nonchalant, haughty and aloof. (See references 2, 5, 7, 13–17, 25, 31, 34, 35, 38, 43, 47, 48*a*, 55, 57, 58, 64, 68–71, 78, 80.)

All observers have in various ways described these people as "immature." This has generally referred to the prominence of dependent attitudes, to their restricted capacity to tolerate frustration, to their relatively low capacity to assume responsibility in family or work, to their sexual immaturity, to the restricted character of their relationships with people. One is less likely to find among patients with ulcerative colitis a person who was highly successful before the illness began. Some patients give an outward appearance of energy, ambition and efficiency but this usually proves to be a thin veneer which hides unreasonable feelings of inferiority, an acute sense of obligation, a need to achieve some sense of security.[80] They avoid chances or dealing daringly with their environment. Such people are often admired for their virtue, morality and high standards.

Although descriptions and case protocols in the literature leave the impression that this characterization of the ulcerative colitis patient is accurate, there are few figures of actual incidence. I found obsessive-compulsive character traits to be prominent in twenty-six of twenty-seven patients. None, however, had a well developed obsessive-compulsive neurosis, and all showed some to considerable decrease in some of the obsessive-compulsive traits during the active illness. Twenty-three of twenty-five were ingratiating, placating, submissive, attempted to make an acceptable appearance, were very sensitive, avoided direct demands and had low self-esteem. The other two patients differed from this description mainly in being more petulant, querulous and overtly demanding. Wittkower[80] classified forty patients into three groups. Twenty-three patients were rigid compulsive characters with a strong sense of inferiority. A second group of twelve, all women, differed chiefly in a more overt display of stormy emotions, were more noisy, petulant, argumentative and exhibitionistic but in other respects resembled the first group. Five patients fit in no consistent group but showed much social anxiety, were shy, depressed and terrified of transgression.

Comment: In recent years attempts to establish typical personality profiles have fallen into disrepute, since usually only the more manifest character traits are considered and dynamic factors are not recognized. Yet this attitude may go too far in underestimating the value of this type of data as a source of information indicating certain dynamic trends. With better understanding of the factors involved in character formation one not only may find clues to common dynamics but also to factors which may be covariant to both the psychic and somatic processes. It would be misleading to say that the character traits here listed are specifically associated with ulcerative colitis. Most people with such character traits do not have ulcerative colitis. But given the diagnosis of ulcerative colitis, the possibility of describing the major character traits of the patient without even seeing him is excellent.

Relationship with People

Patients with ulcerative colitis also reveal a rather consistent pattern of relationship with people. On the one hand they appear to have a quite "dependent" relationship on one or two persons, on the other hand they seem to lack the capacity to establish warm, genuine friendships with others.

In the literature this has been described in such terms as "dependence," "overdependence," "infantile dependence," "abnormal attachment," "ambivalent dependence," "parent controlled," "fixation on parent," "symbiotic relation." (See references 1, 2, 5–7, 9, 13–17, 25, 31, 34, 35, 37, 38, 41, 43, 48*a*, 50, 51, 55, 57–59, 64, 66, 68–71, 78, 80.) In most instances this intense relationship is with a parent or a parent substitute. Many of the writers point out that, if and when these patients marry, the spouse often fulfills such a role. Lindemann[42] has placed particular emphasis on the key role of some per-

son in the psychosocial orbit of the patient. He describes this person as one whose presence in the orbit of human relationships is indispensable for the patient. Sperling[67] (speaking of "psychosomatic" cases in general and not ulcerative colitis alone) described the patient as living "in an emotional symbiosis with one object in the environment, who does not have to be the actual mother but who somehow, in the patient's unconscious, serves the dynamic function of a mother figure."

Lindemann's[41] reference to the role these key figures play in the psychosocial interactions of the patients points up the other aspect of the kinds of relationships these people have, namely, that they have difficulty in initiating social interaction except through the key figures. This is descriptively recorded in observations that these patients do not readily form friendships, they often are on the periphery of social groups, in which they feel uncomfortable and ill at ease. They may be shy, seclusive, stiff and formal. They may have many acquaintances but few intimate friends. Some feel distinctly estranged from people.

Examination of our own clinical material as well as of case protocols in the literature allows for further delineation of the nature of the key relationships. One gains the impression that the patient lives through the key figure (i.e., mother) and the key figure lives through the patient. Seen from the side of the patient, the patient appears to depend on the key figure as part of his equipment for dealing with the external world. This is revealed by their leaning on the key figure for guidance, advice and direction; by their reluctance to take initiative or to plan independent action; by their tendency to act out wishes, conscious and unconscious, of the key figure, or to live vicariously through the key figure; by their use of this individual as a barrier against or protection from threats from other sources; and by their need to please and placate this figure and to protect her from anxiety or other unpleasant affects, whether provoked by the patient or by others. At the same time the patient's attitude is a highly ambivalent one. The patient is extremely sensitive to, but often frustrated by, the demands of the key figure, but finds it impossible to relinquish his own parasitic relationship. Similarly the demands and requirements of the patient at times are unmet, or only conditionally met, with consequent intensification of the conflict.

In some instances a subordinate figure comes into the relationship. The function of this person is sometimes a buffer one, to absorb the hostility of the patient and of the key figure; sometimes a substitute one, who fulfills much of the same function as the original figure; and sometimes an auxilliary one, to please and gratify the key figure. The choice of spouse is frequently determined along such lines.

Revealing insight into the nature of the object relations comes from observations of the doctor-patient relationship. It is a general experience that the patient either becomes very "dependent" upon the physician or establishes no or at best a very superficial relationship. It is also general experience that patients who develop such a "dependent" relationship, whether or not it is consciously planned by the physician, do better than patients who do not. Of the nine patients who died among my total group of thirty-nine, eight were never able to establish a relationship with me or any other doctor concerned in their care and one had a prolonged relationship (four years) which was unexpectedly interrupted. None of these eight patients was in such critical condition at the time of initial contact that this could account for either the failure to relate or the death. Once a relationship has been established it is unusual for the patient to relinquish it and remain in good health. The patient may leave the doctor because of negative transference conflicts but this is generally accompanied by a relapse, unless a substitute had already been acquired. Any interruption of the doctor-patient contact, especially early in the relationship, is likely to be accompanied by some relapse of symptoms. I have utilized the circumstance of rather frequent one to three day trips out of the city as an opportunity to observe the effects of such enforced separations on hospitalized patients. In general the response is a worsening of symptoms but a denial by the patient that the break in doctor-patient contact was of any importance to him. Eventually, with the doctor's encouragement, the patient may be able to speak of his feelings about such separations and become more tolerant of them. But even under these circumstances it is noted that the patient may use realistic or magical means to maintain a sense of continuous contact with the absent physician. A telephone number and the assurance by the physician that he can be reached in the distant city often suffices, even though the

patient never actually phones. One patient for a whole year carried an unfilled prescription for paregoric, feeling secure in the knowledge that if she could not reach me she had the prescription. Although such situations arose several times, it sufficed for her to think of the prescription to enable her to feel she was in contact with me. Consistent with this is that when the patient has such a relationship, pharmacologically inactive preparations may have striking symptomatic effects, whereas during negative relationships the most potent agents may not only be without effect but may provoke violent symptoms.[21,22]

Mothers

There is also an impressive consistency in the description of the mothers of patients with ulcerative colitis, although there are differences in how the women describe their mothers as compared to how the men do. (See references 5, 6*a*, 9, 10, 13, 15–17, 22, 25, 28, 31, 34, 37, 38, 43, 44, 46, 50, 51, 55, 57–59, 65, 67, 69.) It is important to emphasize that the bulk of data on the parents comes from patients' descriptions; there are no systematic or direct studies of parents of patients with ulcerative colitis, although some information is available from those who have worked with children.[28,57,58,59,66]

In general, the mothers are described as controlling and dominating. The women are more likely to think of their mothers as powerful and overwhelming figures, who make them feel helpless and dependent. They often describe their mothers as cold, unaffectionate, punitive, rigid, strict and judgmental. The men, although describing similar domination, are much more likely to find it acceptable and to describe their mothers as kind, considerate women who worried constantly about their well-being. Despite these differences in attitudes of the men and women toward their mothers, one readily finds many similarities among the mothers. In general they are either unhappy, pleasureless, gloomy women, with no great zest or enjoyment in life, or hard driving perfectionistic women who are constantly dissatisfied with their own or others' accomplishments. They tend to be worrisome, complaining, pessimistic, and often hypochondriacal. A high proportion show moderate to severe obsessive-compulsive traits, a smaller proportion show pathologically disorderly behavior or eccentric preoccupation with collections of odds and ends. A few are psychotic characters or frankly psychotic, usually paranoid. Included among the latter are religious zealots with powerful feelings of right and wrong and hell and damnation, food faddists and self-righteous, self-appointed guardians of public morals. Many mothers are described as having depressions.

A prominent feature, described in different ways by many patients, is the mother's propensity to assume the role of a martyr. This includes the mother (usually described by a male patient) who devotes herself selflessly to everyone, sacrifices herself, suffers humiliation and hardship, all for the health and welfare of the patient; the mother who displays and demonstrates her martyrdom to her family, mobilizing guilty reactions from the patient; and the mother who approaches religious and social martyrdom in her public display. One is left with the clear impression that the majority of the mothers are masochistic characters and that the relationship between mother and patient is very much determined by this. The patients appear to be extraordinarily "in tune" with the shifting dynamics of the mother's needs, anxiety and guilt. This is particularly evident in the response to non-verbal cues. Many patients comment on their sensitivity to mother's sigh, look or change in posture or facial expression. Some patients, particularly the men, submit passively and obediently to the mother's domination, while others, also submitting, do so with the complaint that mother won't permit them to do otherwise.

Several authors[6a,14–17,25,66] have been impressed with the unconscious gain to these mothers to have their children sick. Not only does it seem to assure complete dependence and submission but also an opportunity for the gratification of certain sadomasochistic needs. The reciprocal gain for the sick patient is obvious. This is well illustrated by the statement of a twenty-two year old woman about her mother: "She always had to inspect and regulate, so that when I became sick it was very gratifying to her. She took pleasure in the diet and was completely preoccupied with doing the right thing. She penetrated into all levels of control, even to regulate my bowel movements. Her health was never better than at that time." It is notable how many mothers insist on taking care of their sick adult sons or daughters even when there are others to do it.

The quotation just cited also tells something

of the nature of the control sought by the mother and by the patient. Sperling[65–67] uses the term "emotional symbiosis" to characterize this relationship. Some patients in analysis have actually verbalized that they feel like a physical appendage to mother, as if an organic unity existed. In many spheres of living they literally abdicate any sense of individuality and personal participation and act as a proxy for the mother, enjoying only what she would enjoy and forever seeking assurance that no transgression had taken place. This perhaps is responsible for the common description by patients of their mothers as "unpredictable." It is the patient who needs constantly to know what mother's needs and wishes are at every moment and any unanticipated behavior is felt by the patient as inconsistent, quixotic, impulsive and dangerous. Yet there is evidence to indicate that some of the mothers, certainly the psychotics and psychotic characters, truly were unpredictable and inconsistent to a high degree. In any event the patients' technic to deal with mother is markedly colored by attempts to anticipate and fulfil mother's wishes, to alleviate mother's anxiety and guilt, and to manipulate other people and situations so that even outside factors will not upset mother. In other words, he "learns" the conditions under which he will not be rejected.

Comment: It is again necessary to emphasize that the bulk of the information about the mothers comes from the patients. It is difficult to know whether the consistency in the descriptions of the mothers and of the mother-patient relationship is a reflection of the common psychology of the ulcerative colitis patients or whether it truly indicates a close similarity of these mothers. I am inclined to believe that both factors play a role. Sperling,[65,67] Prugh[57,58] and Gerard,[28] who have studied children and hence have made direct observations on the mothers, described them as rigid, inconsistent, at times overindulgent, at times overwhelmingly dominating, extremely ambivalent and lacking in maternal qualities. Sperling[66] in particular stressed strong unconscious destructive impulses toward the child and her need to keep the child in life-long dependency for the gratification of vitally important bodily and emotional needs. Gerard emphasized also the mother's ambitiousness for her child's achievement, pushing the child for independent but conforming behavior. The one mother I have studied directly was an extremely perfectionistic compulsive woman who warded off anxiety by demanding constant achievement from herself and her family, but especially from her oldest son, who developed colitis. Nonetheless, analytic observations of patients with ulcerative colitis leave little question that many of the characteristics ascribed to the mothers have been contributed to quantitatively, if not qualitatively, by the patients' own projections.

The descriptions of the mothers and of the mother-patient relationships clearly provide a basis for the characteristic relationships already described. The "key" relationship usually is with the mother or a mother surrogate.

Fathers

It is remarkable how much less information is available about the fathers than the mothers. Many protocols barely mention the father and some do not refer to him at all. Among my patients in analytic psychotherapy far more time was spent by the patients on material about the mother. In many instances only a very shadowy, stereotyped picture of father was obtained, and that chiefly on direct inquiry. I believe the sparsity of information about the father is a reflection of the lesser role played by the father in the development of these subjects.

In our material as well as in the literature there is some difference in the descriptions of the fathers of the women as compared to the men. (See references 2, 6*a*, 9, 10, 13, 25, 31, 34, 35, 38, 43, 44, 55, 69, 78.) In general women are more inclined to present their fathers as gentle, kind, passive, usually ineffective men to whom they are quite attached, while the men are more likely to describe father as brutal, punitive, threatening, coarse and very masculine. There are a number of exceptions on both sides. Thus some of the women's initial descriptions later changed to indicate a more aggressive, rigid, punitive man. That the relationship with father also had sadomasochistic overtones is revealed by the complaints of some women, usually later in therapy, that the father was too lenient. Men patients tended to see the fathers as threatening and abusive to the mother, who suffered thereby, and with whom the patient identified. The man often seemed to feel that the father regarded him as a "sissy." The women, on the other hand, often complained that the father did not adequately protect them from mother's aggression. The father was particularly likely to be described

in positive terms when he had died while the patient was still a child.

Objective data on the fathers are not available and the impression of any consistent pattern is not to be found. Among them we find alcoholics, passive inhibited characters, psychotics (usually paranoid schizophrenics), eccentrics and obsessive-compulsive characters. We cannot support Brody's[6a] statement that the fathers are usually healthy men. The important finding is that the father is so often so inconspicuous in the patients' accounts.

Siblings

Of note here is only that the siblings are so often described as more outgoing and uninhibited (even when they are not) and as having a favored status with one parent. Often the complaint by women patients is that a brother is favored by mother even when he is not so considerate of mother as the patient. Men patients may say a brother is more accepted by father because he is more masculine.

Sexual and Marital Adjustment

All data available support the conclusion that the sexual development of these patients is inadequate. (See references 2, 7, 8, 11, 13, 15–17, 25, 31, 34–38, 43, 47, 50, 51, 55, 59, 64, 65, 67, 69–71, 78 and 80.) In terms of overt behavior, interest and participation in sexual activity is low. Most of the women are frigid and even those who experience orgasm do so but rarely. A good number of men and women remain with little or no heterosexual experience even when married. The men who are not impotent have a rather desultory interest in heterosexual activity. The man often assumes a passive role in relation to his wife, who may be the one to initiate sexual activity. One sixty-one year old man had intercourse with his wife only three or four times in more than thirty years of married life, all within the first year. I have not yet seen or read of a man or a woman with ulcerative colitis who had enjoyed a vigorous, hearty, active sexual life. Many patients acknowledged a wish to be fondled or cuddled, really like a child, but at the same time were totally rejecting any genital approach.

They are prone to regard sexual activity in anal terms. They use terms as dirty, soiling, digusting, unclean, etc., and they feel squeamish about body contact, secretions and odors. Many feel obliged to bathe immediately after a sexual contact. Rigid moral standards are common. Such attitudes often reflect the mother's attitude. Ascetic rationalizations are not infrequent. Latent homosexual trends are apparent among some of the men but I have not yet seen or read of an overt homosexual who developed ulcerative colitis.

Many patients with cecostomies or ileostomies are observed to derive erotic gratification from manipulation of the stump.[25,45,46,64] In some instances, patients replace genital masturbation with manipulation of the stump, which shows tumescent responses, and then enjoy conscious sexual fantasies, sometimes homosexual. Other patients show an intense preoccupation with cleaning, wiping and manipulating the stumps, but without admission of conscious sexual feelings. It is not yet known whether this erotization of the artificial opening is more prominent among the ulcerative colitis patients than among others.

The marital rate is probably not different among this group of patients than it is in the general population, although actual figures are not available. Among the thirty patients over twenty-five years old in our series, all but four were or had been married. In most instances the characteristics of the marital relationships could be predicted from the nature of the object relationships and sexual adjustment, which have already been discussed. In some instances the husband or wife really fulfilled the role of a succoring, sustaining mother. More often the spouse took a subordinate role to the mother and occasionally was the latter's conscious or unconscious choice. Not infrequently it was the mother-in-law, who closely resembled the mother, who was the real object, the spouse being treated more like a sibling.

Pre-morbid Bowel History

Although many writers have speculated on the significance of early bowel patterns and training experiences among these patients, there actually is remarkably little information on this point. Elsewhere we have reported that a high proportion of our patients suffered from constipation prior to the development of the colitis and that this often had its inception in childhood.[19,20] No reliable information is available as to the age and character of toilet training of these patients. Gerard,[28] reporting on eight cases among children, states that in all cases bowel training had been early and punitive. Prugh's[59] studies

indicate that while early and coercive bowel training was common among patients with ulcerative colitis, it was not a major factor in the absence of associated personality disorder. Lindemann[42] found a confirmed history of severe toilet training in only two of forty-five adults but many factors make the securing of an accurate history difficult.

Childhood material indicative of intense conflictful relations with the parents regarding bowel activity is prominent in the histories of some patients and totally absent in others. Thus some patients tell of the mother's or father's intense interest in and control over their child's bowel movements, the punitive or seductive administration of cathartics or enemas, coprophilic and soiling acts as a child, bowel activity in response to parental pressure or conflict. (See references 2, 7, 13, 25, 31, 32, 50, 51, 57–59, 70, 71.) Yet more published protocols make no mention of such material and some patients emphatically deny their occurrence. It is perhaps significant, however, that among our patients the longer the patient was in therapy, the more likely was such material encountered. Nonetheless, it cannot be said at this time that the data available indicate a very intimate relationship between overt childhood excretory behavior and the occurrence of ulcerative colitis. Different kinds of data are necessary to settle this point.

Precipitating Circumstances

The identification of the somatic processes which are pathognomonic of ulcerative colitis makes it possible to establish more precisely the exact time of onset of the disease in many cases and thereby to examine the circumstances under which the disease becomes manifest. Elsewhere we have pointed out that the presence of blood in the stools is the most common initial symptom, often preceding diarrhea.[19,20] This is generally true when the disease begins in the distal left colon, the most common initial locus. When the process initiates in the right or transverse colon, diarrhea and cramps without gross blood are usually the first symptoms. In establishing exactly the onset of the disease it is necessary to inquire into the first clear deviations from usual bowel activity. Many patients are found to have had rectal bleeding or abrupt severe constipation for days, weeks or even months before diarrhea begins. When the onset of disease is so established, we find that the time interval between a psychologically stressful circumstance and the onset of the first symptom of the colitis often is a matter of hours or a day or two. On the other hand there are cases in which the onset is rather gradual and not easily timed and in which one deals not with a well defined stressful experience but rather with a gradually changing psychic status, during which symptoms gradually and sometimes intermittently develop. (See references 2, 7–11, 13–15, 19, 20, 31, 35, 37, 38, 41, 44, 57, 58, 64, 66, 70, 71, 78.)

In our series the onset was precisely established in thirty patients who were also studied psychologically. The following kinds of onsets were observed.[19] Ten patients noted blood as the first symptom, with diarrhea coming on later or not at all. In five of these the onset was associated with a discrete event concerning which the patient was consciously disturbed and the bleeding followed within days. In one case there was an abrupt onset of bleeding following a New Year's party, but the significance of this was not elucidated. The bleeding began gradually in a girl during adolescence, and in a thirty-one year old man during his wife's first pregnancy. In two adults the first episodes of bleeding occurred in childhood and no memories of the circumstances at the time of onset were available.

CASE REPORTS

CASE 1. A thirty-one year old woman became pregnant a few months after the birth of her first baby. Two years earlier, when she discovered her husband was having an affair, she separated from him and returned to her mother. After six months a reconciliation was accomplished, although the mother was pessimistic of its outcome. The patient decided that having a baby would help hold her husband and the first child was conceived in this setting. When she found herself again pregnant a few months later, rectal bleeding began. Stools remained constipated and bleeding continued for six months and then diarrhea developed. The patient thought that a second pregnancy so soon was too much and that her husband might again leave her.

In seven patients ulcerative colitis began with bloody diarrhea. Three of these showed an abrupt onset in settings in which the patients were consciously disturbed. Four of them began during or just before adolescence (ages twelve

to sixteen); in one boy this began soon after the death of his mother and in one girl while the father was depressed.

CASE II. *Bloody diarrhea:* A twenty-nine year old woman married when she discovered she was two months' pregnant. She hoped to hide the premarital conception from her puritannical mother by saying the baby was born prematurely. Gestation actually was seven months so the baby was born five months after the marriage. Two days after the baby was brought home and her mother arrived to help the patient had abrupt onset of chills, fever and diarrhea which became grossly bloody in a few days.

Five cases began with abrupt and severe constipation, usually associated with severe rectal or lower abdominal pain, and followed in a few days by bloody diarrhea. In four of these patients this followed within hours or days of an upsetting event. No clear-cut precipitating event could be elicited in one interview in the fifth case.

CASE III. *Acute constipation:* A twenty-one year old married woman was awaiting the return home of her soldier husband, whose train reached the city that day. After keeping her waiting several hours while he visited his mother, he appeared at the door, and without further elaboration announced that he wished a divorce. On this note he left. The same day she was seized with terrific cramp-like pain in the left lower quadrant, an urge to defecate, but inability to do so. She was admitted to a hospital where she was given eight enemas in two days before any relief was achieved. Following this she had formed stools, three to four times a day, for a month, and then small amounts of blood were first noted. Thereafter she passed blood and mucus four to five times a day, stools became semiformed, and then grossly diarrheal and bloody.

Four cases began with bloodless diarrhea of fairly abrupt onset. In a thirteen year old boy diarrhea developed just before his bar mitzvah, an event which he prepared for under great pressure from his mother. In three no discrete precipitating event was disclosed but rather a change in over-all psychologic adjustment. One patient lost her father and then over the next ten months felt her relationship with mother threatened by shifting alignments in the family. A man took over his father's business at a time that his wife was pregnant for the second time. A third, after many years of attempting to cope with a psychotic mother, herself began to feel estranged and depressed, then developed diarrhea and fever, with a feeling of "relief" to be sick. In all three cases the patients believed they were obliged to accomplish more than they were able to do.

Four patients showed very mild diarrhea or intermittent bouts of diarrhea for several months or years before ulcerative colitis was finally diagnosed. In three this began first before or during adolescence.

CASE IV. *Insidious diarrhea:* A fifteen year old girl noted over a period of two months a gradual increase in the frequency of her bowel movements which, however, remained formed but soft. During this time there was increasing turmoil over her changing status as an adolescent. She was then in an automobile accident, which involved no serious injury but did represent a disastrous outcome of an attempt to identify with her adolescent peers. Immediately after the accident her bowel movements became watery and frankly bloody.

The case reports in the literature and our own data indicate clearly that the mucosal reaction may occur within hours or days of events which abruptly upset a precarious psychic balance or more gradually during periods of changing psychic equilibrium. While such a close time relationship between the disturbing events and the onset of symptoms strongly suggests a relationship between the two, the interpretation of the meaning of the "precipitating" event presents more difficulty. For convenience I will consider first the cases in which the event was distinct, with the onset promptly thereafter, and then the cases in which the disease began over a more gradual period of psychologic change.

In my series there were sixteen cases with acute onset in which well defined events immediately preceded the bleeding. Eleven began with bleeding, with and without diarrhea; four with acute obstipation followed by bleeding; and one with diarrhea without gross blood. Summarizing the data, the following phenomena were noted: (1) real, phantasied or threatened interruption of a key relationship; (2) demands for performance which the patient felt incapable of fulfilling, especially when support had been withdrawn or when disapproved activities were involved; (3) overwhelming threat from or disapproval by a parental (usually) figure. Common to all these circumstances was that the patient acutely felt helpless to cope with what

was happening and previous psychologic defenses, such as compulsive mechanisms or magical thinking, crumpled.

The cases in the literature with acute onset follow closely the same pattern. Murray stressed sexual problems, which are indeed prominent among many patients, but the immediate precipitating events were ones which overwhelmed the patient with helpless despair.[50,51] Groen stressed that the precipitating situation in his six cases, all of whom had an acute onset, was one with which the patient could not cope, involving an acute love loss and a painful humiliation.[35] He stressed the helplessness of the patient. In all of his cases an actual or threatened separation occurred. In two of the cases an intensification of compulsive and phobic symptoms preceded the final break. The cases of Jackson,[37] Karush,[38] Cobb[9] and Small[64] began after separations. Grace's two cases of bleeding and one of diarrhea began soon after separations while the other case of diarrhea began when the patient's attempts to achieve a response from his mother by gifts and performance failed.[31] Prugh's nine year old patient bled after being ousted from his mother's bed by his returning soldier father.[57,58]

In the cases beginning insidiously, usually with slight bleeding or mild intermittent diarrhea, one usually deals not with a clear-cut precipitating event but rather with a period during which mounting pressures threatened previous psychologic compensation. In many cases, after months or even years of such mild and intermittent symptoms some event acted as "the straw that broke the camel's back," precipitating the full blown syndrome. Ten of our cases fit into such a group. Four began during adolescence. Two men and two women developed symptoms during periods of mounting responsibilities associated with marriage and the birth of children, while relations with supporting parental figures were disturbed, and two became ill during severe psychiatric illnesses of parents. The cases in the literature also follow this general pattern.[8,31,38]

Comment: The significance of the precipitating events or circumstances begins to have meaning in terms of the processes already discussed. At the risk of a premature and oversimplified generalization, but in order to focus attention on problems that will require further clarification, I suggest the following factors to be necessary, but not sufficient, conditions for the development of the somatic condition. (1) The important interpersonal relationship (or relationships) which has been an integral part of the patient's total adjustive process becomes less effective. (2) The pressure from instinctual forces, all at a pregenital level, becomes relatively or absolutely (e.g. in adolescence) stronger. (3) The character defenses, already described, become inappropriate or inadequate under the circumstances. (4) The patient is increasingly thrown on his own resources for performance. It is to be noted that these four factors are mutually interdependent. Other investigators have stressed one or another of these aspects of the dynamics of the precipitating situation. Groen stressed the acute love loss and a painful humiliation.[34,35] Grace spoke of the importance of symbolic rejections or a threat to a dependent position.[31] Paully spoke of the precipitating circumstance as anything threatening the patient's dependence.[55] Daniels described precipitating situations as those in which there is a serious threat to security.[15] Lindemann laid major emphasis on loss of security, especially loss of another person of emotional significance, a sudden decrease in rate of interaction.[41] Among his eighty-seven cases, seventy-five occurred after a bereavement, two occurred after loss of cultural milieu, six occurred with threat of psychoses and four occurred after hemorrhoidectomy. Unfortunately, these interesting data do not include information as to when the alleged precipitating event occurred in relation to the onset or what the presenting symptoms were. Lindemann lays great importance on a "delayed grief reaction." Among thirty-one of our patients fifteen might be considered to have unresolved grief, ten due to deaths. Alexander emphasizes the general psychodynamics of the excremental function as conspicuous in the precipitation of the disease.[1] He states that the first symptoms frequently appear when the patient is facing a life situation which requires some outstanding accomplishment for which he feels unprepared. Karush and Daniels state that the attack began soon after a sudden, unforeseen threat to the security of a precariously effective adaptive system and that, in the face of an emotional blow, there was loss of successful mastery and depression.[38]

It is clear that these points of view are in essential agreement but differ in emphasis. In order to get further insight into the pathogenic process, I propose now to examine the conditions under which relapses occur.

Relapses

Rigid criteria must be established as to what constitutes a relapse. Following the characterization of the somatic process already discussed,[19,20] relapses, for the purpose of this analysis, are defined as *episodes that begin with bleeding after a period of normal bowel activity of a month or more.* Even though some episodes of diarrhea without bleeding and diarrhea that later became bloody obviously are relapses, they will not be included because other determinants, including anatomic factors, may be involved in the genesis of the diarrhea and cannot be clarified by the kind of information available to us.

Using such criteria we have data on thirty relapses among ten patients. One patient, observed over five years, experienced seventeen bleeding episodes, most of them mild and short-lived. Twenty-four episodes involved real, threatened or symbolic separations or anniversaries of such. For all of these some behavior of the patient or some external event seriously reduced or threatened to reduce the effectiveness to the patient of a relationship and as a consequence the patient actually or in fantasy felt a loss and under pressure to assume more independence. In all of these instances the patient felt unable to do so and in this setting the bleeding began. The six exceptions, not directly involving separations, provide interesting confirmation. In all the patient found himself in a situation in which he felt endangered or enraged but felt powerless to do anything. The common denominator to all the bleeding episodes appears to be a feeling of relative helplessness.

It is difficult to evaluate relapses in the literature from this point of view since most protocols do not provide sufficient data either as to symptomatology or as to the circumstances. However, I consider the following reports to include examples which might be regarded as confirmatory of my data: references 35, 31, 2, 78, 14, 47, 65, 66, 38.

Affective Status

The data on relapses immediately focus attention on the affect experienced by the patient at the time of onset and during relapses. For present purposes we are dealing with the affect which enters consciousness, recognizing that this may not be the original one but a multi-step elaboration. The identification of the affective status is made from direct observation of the patient's behavior, from the verbal content during interviews or therapeutic sessions, and from the patient's own description of how he felt. Data are available on affect during forty-five onsets and relapses among sixteen patients. In all instances the feeling tone at the time of symptoms development was designated by such expressions as "helpless," "despair," "hopeless," "overwhelmed," "too much to cope with," "too much to expect of me." In general there was a fairly good correlation between the severity of the symptoms and the degree of helplessness or hopelessness felt by the patient. In one case this affect was covered by the opposite behavior; the patient intensified his activity and work and for several weeks denied both symptoms and affect. When he could no longer deny the presence of bleeding, he was plunged into an abyss of despair and bleeding became massive. In many instances these feelings merged into depression, with added qualities of being alone, bereft, deserted, unwanted, unworthy. It was notable that conscious anger, even if inhibited or denied, did not precipitate an attack unless it was followed by a feeling of helplessness and despair.[21]

Examination of the literature reveals no systematic attention to the affect preceding the onset or relapse of ulcerative colitis. None of the writers has made an adequate distinction between relapses and the reactions of the chronically diseased bowel. Thus it is difficult to evaluate either their interpretations or their protocols in terms of identifying whether any affect was consistently associated with the onset of the disease or with relapses as I have defined them. Lindemann mentions helplessness, sorrow and depressions as the emotions associated with attacks.[41,42] Groen defines the affect as humiliation and defeat.[35] The protocols of his cases include such descriptive expressions as "disappointed," "lonely," "humiliated," "miserable," "absolutely crushed," "powerless," "shocked," "hurt" as preceding episodes of bleeding. West describes his patient's "inability to secure himself against injustice."[78] Sperling notes the extreme helplessness experienced by the two children she studied.[66] Grace says the attacks occur in settings of anxiety and resentment, when the patient feels frustrated, humiliated, angry and resentful. Their protocols indicate helpless, despairing attitudes.[32] One of Appel and Rosen's cases felt "humiliated" when his sisters left.[2] Cushing noted "bowel symptoms"

to develop when control was threatened.[13] Karush and Daniels noted in one of their analyzed patients that when she was "overwhelmed by fear, hopelessness and despair," bowel bleeding or diarrhea would follow.[38]

Some writers stress "fear," "anxiety" and "apprehension"[43,50,51,69] while others emphasize "rage," "resentment," "anger"[55,57–59,64–67] but none of these terms is sufficiently supported by the data presented to allow for critical comment.

Comment: The discovery that the episodes of bleeding are consistently associated with a feeling of helplessness or despair is an arresting observation but before any conclusions are drawn I propose first to examine what other psychosomatic disturbances are manifested by these patients as symptoms alternative to bowel symptoms and what affect, if any, is associated with such symptoms.

Alternative Symptoms and Associated Affect

Headache. By far the most common alternative symptom experienced by patients with ulcerative colitis is headache, although this seems to have escaped the attention of most observers.[21] Among twenty-three patients in whom adequate histories were obtained twenty suffered from headaches. In fifteen the headaches were severe enough to have required medical attention. Seven patients had headaches as a major symptom before ulcerative colitis developed. In general, headaches and active colitis did not coincide. Headaches either antedated the onset or occurred during intervals when the patient was relatively free of colitis. Thus of fifty-six headaches only five occurred during a period when the patient was having bleeding or diarrhea. The occurrence of a headache during an attack of colitis was often found to herald the end of the attack.

Ten patients had headaches which clinically appeared consistent with the diagnosis of migraine. Ten patients had muscle tension or hysterical conversion type headaches. Some of the patients who had migraine also had other types of headaches.

Fifty-six headache periods were observed during the therapy of nine patients. The two patients longest in therapy accounted for forty of these. The headache periods presented a striking contrast to the periods of active colitis. On forty-six occasions it was found that the headaches occurred when the patients felt in control, had taken an active stand, made a decision, thought something through, but that this was followed by conscious or unconscious guilt. In none of these instances did the patient feel helpless or afraid. In all of these examples there was evidence of strong conscious or unconscious aggressive or sadistic impulses. In many the patients spoke of the intensity of the thinking process associated with contemplated action. Other observers, including family, doctors and nurses, frequently commented on the unusual "aggressiveness" or "assertiveness" of the patients around the time that the headache occurred. Occasionally the headache occurred on the anniversary of or in response to something symbolic of some previous occasion when the patient felt self-assertive or aggressive.

Four headaches (all of one patient) were not so clearly associated with such identifiable feelings but rather with an identification with the father, who also had headaches. Her headaches were considered to be hysterical and it is perhaps significant that at other times the patient suffered from other hysterical pains. Five headaches did not fit into any identifiable pattern.

Only one headache (of fifty-six) occurred when the patient felt helpless, sad, "unable to solve all these things," wondering if I was trying to get rid of her. Interestingly, she also had diarrhea and anorexia at the same time.

When directly queried, patients were unequivocal in contrasting the headache and the colitis status. They all contrasted the active character of their thinking and behavior before the headaches to the passive, helpless attitudes before the colitis attacks. Conscious and unconscious selfpunitive attitudes were common in association with the headaches.

The literature contains no reference to the occurrence of headaches among patients with ulcerative colitis and I am able to find only three reports which incidently mention headache.[8,38,40] Although Karush associated the headaches "with fluctuations in the intensity of the erotic feelings toward the analyst" there is insufficient information in the protocol to verify the interpretation.[38] It is significant that the headaches occurred in a period when his patient had no bowel symptoms and was more quickly mobilizing and expressing rage at frustrating figures. Furmanski, in a study of 100 patients with migraine, found "colitis" in eighteen (ulcerative colitis in one, mucous colitis in seventeen).[27] Among sixteen patients with mucous or spastic

colitis in my practice, twelve had headaches. Kepecs describes a patient who had diarrhea when compliant, submissive and unable to express anger, and migraine when aggressivity became overt and expressed.[39]

Comment: These data are of interest as indicating different levels of psychologic function corresponding to the two kinds of somatic symptoms. It renders untenable the concept that ulcerative colitis is simply the way in which these individuals respond to an emotional stress. Rather it indicates that a particular psychobiologic situation is a prerequisite for the development of the bowel disorder. So far, the consistently found affective status of "helplessness" provides the best clue as to what these psychobiologic requirements are. The significance of headache among these patients is the subject of a more detailed report elsewhere.[21]

Upper Gastrointestinal Disturbances. Anorexia, nausea and vomiting commonly accompany attacks of colitis (and may also accompany the headaches). But some patients suffer from such symptoms independently of the colitis. Ten of twenty-three patients had such a history and three dated the symptoms from childhood. Since none of these patients had these symptoms independently of colitis during my observation I have no precise data as to the psychic determinants. In one adolescent boy the nausea and vomiting appeared to be hysterical conversion symptoms. Two women, twenty-five and eight years before the colitis, each had a period of extreme anorexia and weight loss, clinically resembling anorexia nervosa, but in both cases this information was only obtained from other sources (old chart and family) and was not revealed by the patient.

One woman gave a history of a peptic ulcer before the colitis, said to be confirmed radiologically, and one man had symptoms suggestive of ulcer but none was demonstrated by radiologic examination.

The literature contains very little information. One of Grace's[31] patients had frequent vomiting in childhood, and Szasz[72] reports one patient who also had a peptic ulcer. In the latter patient the two syndromes never occurred at the same time.

Skin. One patient had eczema in childhood, one had urticaria, one had generalized pruritus, and one pruritus ani—all before the first attack of colitis.

Mahoney's[43] patient had severe eczema, Karush's[38] patient developed angioneurotic edema during analysis, and Kubie's[40] patient had an episode of severe generalized dermatitis. Sperling's[66] patient developed a leg ulcer.

Miscellaneous Manifestations. Among my patients the following manifestations were observed; one patient had hypertension, Ménière's syndrome, facial tic and hayfever; four patients had ulcers in the mouth; one patient stuttered, one had hyperventilation syndrome, another arthritis, two had globus, one showed accident proneness and back pain, and one had had rheumatic fever.

The literature adds examples of toxemia of pregnancy,[70] paroxysmal tachycardia,[14] asthma,[14] ureteral spasm,[13] vasodepressor syncope,[13] obesity,[43] rheumatic fever,[38] thyrotoxicosis[38] and leg ulcer.[66] While all these presumably represent random, incidental disturbances, experience with headaches, the frequency of which escaped my attention as well as that of other observers, leads me to believe that future study should give greater attention to the true incidence of these other disturbances as well as to the circumstances under which they develop.

Gross Psychopathology

Clinical Depression. I have already commented on the fact that some degree of depression is generally evident during active colitis. Alternation of mood from depression to mild elation commonly correlates with the magnitude of bowel symptoms and many patients described such mood swings to precede the onset of colitis. Grace et al. disagree with this and state that "subjects with ulcerative colitis may become constipated when depressed" and "it is well recognized that subjects with ulcerative colitis who enter into a period of psychotic depression lose their symptoms of bloody diarrhea."[31] They cite the case of a man whose ulcerative colitis became quiescent when he became seriously depressed but bring no additional clinical evidence in support of the statement.

Two psychotic depressions were observed among my patients. Both occurred simultaneously with a relapse of colitis. One patient was given electric shock treatment and both the depression and colitis disappeared. The second patient died from massive hemorrhage before any treatment could be instituted. The patients of Cobb and of Tunis also had active colitis and

psychotic depression simultaneously.[9,74] Daniels[14] and Lindemann[41,42] also discuss depression as associated with colitis.

Paranoid Disorders. There is general agreement among those who have discussed the problem that delusional and projective mechanisms are the most common features of the psychotic developments in ulcerative colitis.[1,2,14,38,41,42,61,66] The incidence, however, remains unknown. Moses reports an incidence of 20 per cent among patients in analysis.[49] Among my patients, two had acute psychotic episodes occurring some years after the first attack of colitis. Both patients settled into more or less chronic paranoid states, with well organized delusions, and continued to have attacks of colitis and of headaches. It could not be established what, if any, bowel symptoms were present during the acute psychotic periods. One patient, during adolescence and many years before the colitis developed, had the persistent delusion that she had a bad odor. Another patient, during analysis, had several brief periods when she had the idea that her mother-in-law or her husband was trying to poison her but she always was able to convince herself of the unreality of these ideas.

Although there is a general impression in the literature that psychosomatic disturbances and psychotic manifestations have a reciprocal relationship, this is by no means demonstrated in ulcerative colitis.[2,40,61,66,71a] My two patients as well as the two patients reported by Appel and Rosen,[2] and one patient each of Sullivan[70] and Wittkower,[80] showed psychotic behavior and active colitis at the same time. While it is true that in these cases the psychotic behavior seemed to be less manifest during the more severe colitis symptoms, much longer periods of observation are necessary to clarify the relationship between the two processes.

Neuroses. I have already discussed the characterologic features of these patients. The prominence of obsessive-compulsive character traits was mentioned. Yet no patient in my series presented a full-blown obsessive-compulsive neurosis. Only one of Wittkower's forty patients was so described, although fourteen had obsessional thoughts.[80]

Conversion and phobic symptoms are occasionally noted but certainly are not prominent.[14,80] One of my patients had hysterical pain and one of Daniels'[14] patients had hysterical amnesia, pain and phobic symptoms.

Ulcerative Ileitis after Ileostomy

Elsewhere I have discussed the development of a pathologically similar lesion in the ileum of patients with ulcerative colitis.[19,20] In the present series ulcerative ileitis developed in five patients. In three the ulcerative ileitis developed after ileostomy and in bowel which had been demonstrated to be normal at the time of ileostomy. In all three the precipitating circumstances and the affective status were identical with that observed during previous attacks of ulcerative colitis. In the other two patients the time of onset of the ulcerative ileitis could not be established.

There is no reference in the literature to the conditions under which ulcerative ileitis develops. Regional ileitis is a different disorder.[75a]

CORRELATIVE STUDIES

These are of three types. The first is the reporting of occasions when some bowel symptom occurs during observation of the patient and an attempt is made to relate the simultaneous psychologic data to the bowel symptom. The second is the simultaneous psychologic and physiologic study of patients with fistulas. The third is the correlation of symptomatology with psychic status in the course of observations during psychoanalysis and long-term psychotherapy.

Correlation of Symptom and Psychologic Data. Such short-term random observations have been reported by Murray,[50,51] Sullivan,[70,71] Daniels,[14] Groen,[35] Prugh[57,58] and Sperling.[66] They are of dubious value in ulcerative colitis. My experience is that patients do not report with any consistency symptoms experienced in the presence of the investigator. At times the act of announcing or displaying the symptom may be more significant behavior than the symptom itself. Further, when patients are having frequent bowel movements, the coincidence of a cramp or bowel movement in the examiner's presence cannot be interpreted, no matter how dramatic the psychologic material may be, unless something is known of the frequency and distribution of such symptoms over relatively long periods of time.

Fistula Studies. Study of patients with colonic stoma permits simultaneous observation of changes in the bowel and psychologic processes.[32,45,77,79a] Three patients with ulcerative colitis have been studied in this fashion. The significance of these studies for an understanding of the nature of the somatic process has been critically discussed elsewhere.[20] The present

discussion will be confined to an evaluation of the attempts to correlate the psychologic data with the changes in the colon.

Grace studied four fistulous subjects, two with ulcerative colitis.[32] This is a valuable work containing much useful information but it is not without limitations, due mainly to deficiencies in the design of the study and to the way in which the data are presented. Their conclusions are summarized as follows: "Overwhelming life situations provocative of abject fear and dejection were associated with hypofunction of most of the large intestine with pallor, relaxation, lack of contractile activity, and relatively low concentrations of lysozyme in the colonic secretions. Life situations provocative of conflict with feelings of anger, resentment, and hostility or of anxiety and apprehension were found to be associated with hyperfunction of the colon . . ." Sustained hyperfunction was thought to lead to increased fragility of the mucosa and eventually to the changes of ulcerative colitis.

These conclusions are somewhat at variance with what I have just summarized in this report. However, I believe the discrepancies are more apparent than real and result mainly from an overinterpretation of the data. A serious weakness of this study, which significantly limits the conclusions which can be drawn from it, lies in the handling of the psychologic material. Unfortunately the authors do not establish clearly and set down in print what criteria they used for the various psychologic categories (e.g. abject fear, anger, resentment, apprehension, etc.) which are correlated with the physiologic states. This omission is compounded by an extremely meagre reporting of primary psychologic data, leaving the reader without means of examining their interpretations. Thus the important conclusion that "abject fear and dejection" lead to hypofunction of the colon (which is contrary to what would be predicted from the data of this review) actually is supported only by two brief sections[32] (pp. 93, 154) which describe the patient as "mildly depressed" for four weeks. It is said that the intensity of the "depression" varied from day to day and that the colon was most inactive when "hopelessness was most pronounced," but no further documentary data are given as to the nature and dynamics of this state. Further, no information is available as to the dynamics of the doctor-patient relationship at this time. This is an important omission throughout the study. Nowhere is adequate attention given to the significance of the experimental situation as a determinant of this relationship. Much of the material points to the likelihood that submission by the patient to the demands of the research had become a condition, mutually operative, for maintenance of the doctor-patient relationship. This seems most evident in the stress interviews and the painful procedures, in which the patient was angry or anxious, but *helpless and unable to refuse further participation*, lest the relationship with the doctor be jeopardized. It is perhaps significant that one patient without colitis who objected vigorously to the testing of pain response and who refused to have the experiment repeated (in contrast to the colitis patient) showed hypofunction of the colon as a response. Clearly both patients had conflict, but the conflict was handled differently. Indeed, as one examines the available but limited data on the hyperfunction responses it seems likely that the "resentment" or "anxiety," which remained largely unexpressed, occurred in settings in which important relationships, including that with the experimenter, were believed by the patient to be in jeopardy. Most of the protocols also speak of humiliation, embarrassment, feelings of being ignored and neglected, ("who will take care of me?") as associated with what the authors have described as resentment or apprehension.

All this suggests a greater concordance with the anamnestic data reported in this review and points up the importance of complete reporting of primary data if unique studies of this type are to have the lasting scientific value they deserve.

One of the patients reported in the Grace study (Subject C) was also studied by Margolin[45] and Winkelstein[79a] but no data are available. Only the general statement is made that when an outward display of "emotions" was suppressed the mucous membrane "was seen to flush a fiery red and minute petechial mucosal hemorrhages appeared."

Wener and Polonsky studied a twenty-one year old woman with ulcerative colitis who had a transverse colostomy.[77] Their technic of study was essentially the same as that of Grace, and as such is subject to much the same criticisms. Again no consideration is given to the importance of the doctor-patient relationship. The investigators conclude that "reactions to pain, fear, and anxiety produced pallor of the mucosa and inhibition of mobility. . . . " Anger, resentment, and hostility generally gave rise to

hyperemia and engorgement, with moderate increase in colonic contractions. . . . When the patient was especially depressed, angry, or resentful the engorgement and hyperemia of the colostomy appeared to be more pronounced." It should be noted that these writers describe different reactions to anxiety and to depression than do Grace et al. and again we are left with no statement of what criteria were used.

Comment: The studies here reviewed, while perhaps indicating trends, mainly illustrate some of the as yet unsolved difficulties of method and reporting in this kind of research. In my opinion none of these studies successfully overcame these difficulties and consequently the published conclusions must be regarded with caution. Neither the design of the research nor the methods used, physiologic or psychologic, provide either the investigator or the reader with the necessary information to test the validity of correlations. An entirely different research design is necessary to answer these questions, one which will permit statistical examination of data. Such a design has been developed and will be published elsewhere.[25a]

Psychophysiologic Correlations during Psychoanalysis. While the psychoanalytic technic has yielded much valuable information on the psychodynamics of these patients, so far there have not been any systematic attempts to correlate the psychologic and somatic processes during psychoanalytic study. What correlations have been indicated still fall in the category of clinical impressions and require much more careful evaluation before their validity can be established.

A CRITIQUE OF PSYCHOLOGIC FORMULATIONS

Data have been presented to show that processes which can be demonstrated and examined by psychologic technics are frequent, perhaps necessary, but not sufficient conditions for the development of ulcerative colitis. We are now in position to summarize these psychologic data and to examine the various psychologic formulations that have been proposed. In brief, these patients tend to fall into a population group having preponderately pregenital character traits, especially compulsive and dependent features; they show a defect in their capacity to relate to people, with a tendency to retain features of their early mother-child symbiotic relation; there is a failure to resolve this symbiotic relationship, which genetically and dynamically also appears to be related to the distinctive characteristics of one parent, usually mother, who also cannot relinquish this relationship with her child; sexual maturity is not achieved and the patients tend to make marriages which assure continuation of the same kind of relationship; ulcerative colitis develops in settings in which the important relationship in fact or in fantasy is threatened or actually disrupted, when at the same time the patient feels helpless to cope with the new situation; remissions occur when an effective relationship is again achieved; in similar situations, when more effective adjustive mechanisms are operative and when the affect is other than that designated by such terms as helpless, hopeless, despairing, etc., other symptoms, notably headache, rather than colitis develop; there is a vulnerability to psychotic reactions greater than the general population.

These are oversimplified topical statements, the details of which have been developed earlier in this paper, but they serve to focus attention on the psychologic processes which seem important in ulcerative colitis. When the various psychologic formulations are summarized, it will be noted that in general they are in good agreement but that different investigators have tended to emphasize different aspects of the same material. An attempt will be made to reconcile these differences.

1. Alexander.[1] This writer emphasizes the importance of emotional factors which from early life are associated with excremental and alimentary functions. In the precipitation of the disease and of relapses he emphasizes the frustrated tendency to carry out an obligation, be it biologic, moral or material, and the frustrated ambition to accomplish something which requires the concentrated expenditure of energy. This formulation is largely in terms of the psychology of the anal period of psychosexual development. The fact that colitis frequently appears when the patient is facing a life situation which requires some outstanding accomplishment for which the patient feels unprepared is formulated in terms of a regression to that phase of development in which the infant experiences the excremental act as the giving up of a cherished possession on one hand and an accomplishment on the other. In other words, a regression to the anal form of giving or accomplishment may take place. He emphasizes that anal regression of this type is

common in all kinds of diarrhea and in psychoneurotics who do not display any somatic symptoms.

The specific dynamic pattern in diarrhea is formulated as follows: "Frustration of oral dependent longings → oral-aggressive responses → guilt → anxiety → over-compensation for oral aggression by the urge to give (restitution) and to accomplish → inhibition and failure of the effort to give and accomplish → diarrhea."

Comment: In the previous review we presented the evidence that somatic processes having to do with diarrhea are not primary in ulcerative colitis.[19,20] There is therefore question as to whether the formulation related to diarrhea necessarily applies in ulcerative colitis. Nonetheless the facts are indisputable that the anal regressive material described by Alexander is clearly demonstrable in all patients with ulcerative colitis. This apparent inconsistency can be reconciled if we do not require in our formulation that the anal regressive processes have a causative relationship to the primary processes in the bowel. Actually there is no evidence to link the mucosal-submucosal reactions of ulcerative colitis to the psychophysiologic relationships of the toilet training period of childhood. But even without hypothesizing such a relationship, it will be recognized that the conditions under which the disease develops as described by Alexander are also those having to do with the threat to a key relationship. His formulation correctly focuses attention on some of the distinctive aspects of character formation in these patients, but not adequately defined is the matrix in which this personality formation takes place, namely the special characteristics of this particular mother-child symbiosis. It remains to be seen whether and to what degree the prominence of so-called anal traits is contributed to by the developmental aspects of the mother-child relationship and/or by some biologic features of the bowel leading to an early and abnormal emotional investment in excretory function. Seen in this light we consider the unsuccessful attempts to perform as part of the attempt to satisfy the requirements of the key relationship, and the failure to perform as an expression of the helplessness which ensues when the relationship is seriously threatened or cannot be maintained. On the other hand, the possibility remains that anal-regressive emotional stimuli may have something to do with the fact that this particular reaction occurs in the colon, rather than elsewhere, and the probability that once the pathologic process in the colon is operative such stimuli will secondarily influence the function of the bowel. However, there is no evidence that the primary process in the bowel wall has any such substitutive or symbolic meaning. Indeed, there is no indication as to what adaptive function, if any, the primary process in the colon serves.

2. Szasz.[72,73] Essentially similar criticisms of Alexander's formulation of diarrhea, which most certainly apply with greater strength to ulcerative colitis, have been made by Szasz even though he also assumes diarrhea to be the primary process in ulcerative colitis. Szasz's suggestion is that colonic activation and inhibition, leading to diarrhea and constipation, represent the physiologic sequelae of certain alterations in the upper gastroenteric tract, of which the gastrocolic reflex represents the prototype. A critical consideration of this idea from the physiologic point of view, as it relates to the pathogenesis of ulcerative colitis, has been discussed elsewhere.[21] From the psychologic point of view, according to Szasz, mobilization of strong (unconscious) oral-incorporative strivings would be accompanied by constipation while a sudden decrease in such strivings, usually because of guilt feelings, would result in diarrhea. Accordingly, the bowel symptoms do not express any primary psychologic meaning but are interpreted as manifestations of a vegetative neurosis, i.e., as the remote physiologic sequelae of oral tensions.

Comment: This concept did not specifically develop out of a study of ulcerative colitis and is not proposed by Szasz as a formulation for ulcerative colitis. It is important, however, in that it emphasizes the possible role of oral rather than, or in addition to, anal tendencies in this disease. Szasz derived his concept from psychologic data the validity of which is not dependent on the correctness of the gastrocolic reflex concept or its application to the pathogenesis of ulcerative colitis. From the psychodynamic point of view the role of oral (assimilative) processes in the development of the mother-child relationship is well established, and hence Szasz's formula can also be related to how the person deals with the key relationship. Intensification of strong oral incorporative strivings could be expressive of an active attempt to hold on to or restore the relationship, while their disappearance could indicate a weakening or giving up of

the tie. Passive helplessness might be associated with the latter.

3. Sperling.[65–67] This investigator, no doubt because much of her work has been with children, has concentrated on the characteristics of the mother-child relationship. She stresses the contradictory attitude of the mother, who on the one hand unconsciously attempts to maintain the child in a life-long dependence to satisfy her (mother's) own needs, and on the other hand shows strong unconscious destructive impulses toward the child. The latter are particularly likely to become intensified when the child fails to satisfy the mother's needs or when the child's attempts to satisfy these unconscious needs mobilize guilt or anxiety in the mother. The child then becomes the scapegoat for the mother. According to this concept the colitis develops when a change occurs in this specific relationship with mother (or her substitute). Once this relationship is discontinued it will depend upon the patient's willingness and ability to find a replacement for the lost or given-up love object. When the patient is unable to accomplish this, intense frustration ensues, there is an acute increase in destructive impulses, which, however, remain repressed and are discharged through the symptom of bleeding. "The destruction and elimination of the object through the mucosa of the colon (bleeding) would seem to be the specific mechanisms in ulcerative colitis." The feces and blood represent the devaluated and dangerous objects. Sperling believes that ulcerative colitis shows great resemblance in behavior, dynamics and personality structure to melancholia.[66] She emphasizes the degree of sadism turned inward. "The choice of the organ is determined by oral and anal fixations, the colon being the eliminatory organ. The anorexia, vomiting, abdominal pain, diarrhea and bleeding represent expressions of and defenses against aggressive incorporation of the frustrating object."

Comment: Sperling's emphasis on the developmental aspects of the earliest mother-child relationship is one with which this writer finds himself in strong sympathy. Yet much work remains to clarify the details of this relationship and especially whether there are elements specific for the development of ulcerative colitis. Relatively under-emphasized in this formulation is the child's contribution to the difficulties of the relationship. To what degree and in what ways does the original endowment, the biologic constitution, of the child contribute to the peculiarities of this particular mother-child relation?

Whether the mucosal reaction is a pregenital conversion symptom, as suggested by Sperling, is a moot point. As pointed out by Alexander[1] psychologic data alone will not distinguish between secondary symbolic elaborations of bodily processes (e.g. bleeding and diarrhea) and primary psychogenic factors. While the patient may symbolically elaborate the bleeding and diarrhea as "the destruction and elimination of the object," it is not justified to conclude from such psychologic data that the breakdown of the mucosal surface is a direct consequence of destructive impulses turned inward toward the introjected object. This is a psychologic concept, derived from psychologic data, and it remains to be seen whether it can have this kind of pathophysiologic consequence. Present methods do not permit an answer one way or the other, although such an idea gains credence from Seitz's success in provoking exudative skin lesions by hypnotic technics.[63]

4. Lindemann.[41,42] The significance of the loss of a key person and the prominence of morbid grief as a psychic manifestation has also impressed Lindemann. He too points out some of the similarities to melancholia. He offers no hypothesis as to how these processes bear on the development of the somatic pathology.

5. Prugh.[57–59] Working with children, Prugh stresses the reservoir of repressed anger, developing in settings of loss of security, and points out the inverse relationship between symptoms and the expression or acting out in play of aggressive and hostile emotions. He implies that the bowel disorder is in some way related to the inability successfully to discharge aggression, a vegetative neurotic symptom as defined by Alexander.[1]

6. Karush and Daniels.[38] On the basis of the psychoanalysis of two women patients, the initiating and perpetuating psychodynamic factors for these two patients are summarized as follows: "The patients never succeeded in building psychological stability, which normally cushions the blow of a serious loss or frustration. They elaborated a precariously effective adaptive system and, in the face of an emotional blow, the apparatus for effective action required to cope with the emergency was so disturbed that profound anxiety and rage, long suppressed, now threatened to overwhelm them. With such a loss of successful mastery, combined with character-

istic over-reaching ambition, the most common response was *depression.** Instead of acting out hostility toward denying or frustrating figures they were then overcome by a sense of *futility and hopelessness** and retreated further to infantile clinging and dependency." The authors point out the peculiarly intense effect on their psychologic adaptation of the subjective perception of the severe physiologic derangements, with secondary, largely unconscious, elaboration in archaic, symbolic terms. They suggest that the ease with which this type of regressive behavior occurs may be proportional to the intensity of "a constitutional, schizoid, emotional, integrative defect."

They emphasize that the physiologic changes in the colon cannot be discussed in purely psychologic terms and that the psychoanalytic investigation of adults cannot resolve the enigma of "organ selection." They raise the possibility that the same kind of chemical and neurophysiologic defects that interfere with integrative activity of the central nervous system, reflected in disintegrative psychologic responses, also produce the disintegrative behavior on the colon.

Comment: This formulation stresses the crucial importance of depression in ulcerative colitis. It is related by the authors to the dependency in childhood. While the problem of object relations is not specifically discussed, it is clear that the conditions necessary to establish and maintain relationships are important factors in the vulnerability to depression in these patients. In contrast to some of the other formulations they do not attempt to relate directly the aggressive or destructive impulses and the bowel changes, either in symbolic terms or as vegetative discharge, although their formulation would not exclude either possibility.

7. *Groen.*[35] This author sees ulcerative colitis developing when persons with certain character traits are in conflict situations which involve an acute love loss. He stresses the humiliation suffered by the patient as well as the loss of sources of support and the fact that they are unable to cope with the situation. "The repression of this special kind of defeat, the outwardly 'normal' behavior, the finding of a pseudo solution, while the insufficiency of their own personality has been so rudely revealed to them, the carrying on while they were standing in life helpless, loveless, and without confidence in their own personality—all this appeared to belong to the typical reaction of these personalities."

Comment: While this is a good description of some of the manifest behavioral processes in the patient with ulcerative colitis, it contributes little to the understanding of how this development comes about.

8. *Mushatt.*[52] This author suggests that a basic problem is that the relationship to the outside world is made on an oral incorporative level. "This relatedness is expressed through bodily imagery by means of the gastro-intestinal tract, and from this concept the disorganized gastro-intestinal function can be considered both as a preverbal or visceral communication of primitive psychic activity and as a defense against psychic disorganization." He also sees a similarity to melancholia. Prominent in this concept are the distinctive aspects of the oral level of development, namely a kind of fusion in which the individual feels himself a part of the person on whom he is dependent, the dependency characteristic of the very young and helpless child on its powerful parent, and the attitude that the object is an inexhaustible source of gratification. He points out the ambivalent character of the identifications and the tendency to internalize conflicts in relation to the outside world and to express them through the gastrointestinal tract. The individual's difficulties seem to arise from defects in ego development which impair his capacity to relate to people and to master the environment. These defects are made possible by prolonged exposure to an unfavorable emotional climate, initially in relation with the mother, later with the father. The mothers are often unconsciously rejecting or using the child for their own end. "As a result of these circumstances the individual seems basically to be in a state of depression and secondary chronic rage held in abeyance by a suitable dependency relationship. When such a relationship is disrupted the individual feels helpless against the world, depressed and filled with primitive rage. This rage, in turn, arouses intense fear of loss of love and fear of destruction at the hands of the environment. Internally this finds expression in loss of self-esteem, intense guilt, and fear of punishment from an archaic superego." The author attempts no explanation as to how such processes eventuate in the colitis.

Comment: Mushatt's formulation is valuable in that it relates developmentally the symbiotic

* Reviewer's italics.

mother-child relation and the oral-incorporative (assimilative) process whereby this comes about. He is the only writer who has emphasized the defect in ego development implicit in the difficulties in relating to people. Like previous formulations, the significance of loss of object relationship and depression and the similarity to melancholia are brought out.

9. Grace, Wolf and Wolff.[32] These investigators have provided a description of some aspects of the manifest personality and behavior and of the settings in which the disease develops. Other than some very general concepts of "stress" mobilizing an ejection-riddance pattern involving the large bowel, related to feelings of "hostility," "anger," "resentment," "anxiety" or "apprehension," they propose no specific psychologic formulation.

ATTEMPT AT PSYCHOSOMATIC FORMULATION

I make no pretense at being any more successful than previous investigators in achieving a formulation which satisfies all the known facts. Actually there are too many gaps in our knowledge to permit success at this time. My effort, therefore, will be directed as much to indicating the requirements for a formulation, the areas in which further definition is necessary, as it will be to the formulation itself.

In the first place we must identify the structural and functional locus of the disease. It does not suffice to say that this is a disorder of the bowel. It is a disorder which involves particularly the lining surface of the bowel and very possibly those functional components which are necessary to maintain an effective and selective barrier against penetration into the organism. In addition to mucosa and submucosa, this would probably also include the local circulatory systems as well as elements of the reticuloendothelial system. In this regard it must be remembered that the lumen of the bowel is outside the body and that the lining surface, although of entodermal origin, is, like skin, part of the boundary between the body and an external environment. Further, this "external" environment within the bowel must be considered in ecologic terms, since it includes living organisms existing in a dynamic relationship with the human host. The occurrence of disorders endoscopically indistinguishable from ulcerative colitis in some patients receiving antibiotics brings into consideration the processes concerned with the maintenance of a dynamic steady state between these two environments.[75] While little is known of the dynamics of this process, it may be helpful to include in one's perspective the concept that there are conditions in the host under which the ecologic balance is disturbed or the protective barrier fails. This is not a new idea in ulcerative colitis[29] and has also been suggested in amebic colitis.[12] For convenience I shall refer to these as the conditions bearing on host resistance, where I use this term in the broad sense of all processes having to do with the maintenance and integrity of this membrane in relationship to its environment. Needless to say, this might include processes which have psychologic or behavioral aspects.

Having first posed the problem in terms of a limiting membrane between two environments and the tissue components involved, it is also necessary to consider organ function. Here we deal with the eliminative functions, which are largely motor, aided by some secretory activity.*

Embryologically, the lining membrane develops before the muscular coat.[54] The primitive gut begins with the establishment of the entodermal layer within the spheroidal blastocyst. When the mesoderm forms, its splanchnic layer becomes associated with the entoderm. The entoderm gives rise to the epithelial lining while the mesoderm supplies the muscular and connective-tissue layers of the gut wall. The primitive hind gut ends blindly and it is only at about the sixth week that a connection with the outside is established with the proctodeum. Meconium begins to accumulate in the fourth month but coordinated motor function probably does not develop until some time later. Defecation *in amnio* rarely occurs in the human fetus.[79] The eliminative activity becomes coordinated under the control of the vegetative nervous system and

* The resorption of water, leading to formed feces, may be thought of as a special aspect of the eliminative function, one which involves the absorptive functions of the lining membrane. This function develops later than the purely eliminative function. The infant's stool is initially relatively fluid and only over a period of weeks or months finally achieves the solid consistency of the adult's.[30] This is not simply a consequence of the infant's liquid diet but involves a developmental process as well, as is indicated by the fact that liquid diets at later ages do not result in diarrhea. Further, experiences with ileostomy and colostomy prove that this function can be taken over by terminal ileum or proximal colon even at an advanced age. Motor function is involved, both in respect to infant colon and adult terminal ileum or proximal colon, since formed stools do not develop until motility has slowed.

later in childhood comes partially under voluntary control through mastery over striated muscle, including the sphincters, a developmental and learning process. One might thus construct a developmental and functional hierarchy, ranging from the earliest boundary, and later barrier, function to the highly integrated, learned bowel control behavior; from cellular-tissue function to organ function to total human behavior, which has psychosocial components. It is my thesis that different kinds of behavioral and psychologic phenomena are associated with these different levels of organization. The problem now is to see what clarification of these differences is possible in ulcerative colitis, since more than one process may be operative simultaneously in the same person.

While evidence of disturbed bowel function and disturbed behavior around the act of defecation often precedes the onset of ulcerative colitis, it is the tissue change which marks the transition to ulcerative colitis. The major psychologic phenomena which have been found to be associated with this transition are (1) some disturbance in a key relationship, real, threatened or phantasied, and (2) an affective state characterized by such terms as helplessness or despair. I suggest that the helplessness consequent to the disturbance in the key object relationship may be regarded as evidence of a traumatic separation process and that such a state may be accompanied by biochemical or physiologic derangements which permit initiation of a variety of pathologic processes in tissues, including those characteristic of ulcerative colitis. This general hypothesis is based on the clinical observation over many years that a wide variety of major derangements in tissue function and structure seem to occur in settings of disrupted human relationships.[24] From the beginning of life, survival depends on the maintenance and development of the relationship of the child with some adult, generally mother. Ego development can only take place through object relationships. There is a growing body of knowledge concerning the effects of loss of or absence of object on child development. The observations of Spitz indicate that these may include major physiologic derangements.[67a] Loss of object at any time of life poses a major adaptive task. Although not yet studied scientifically, it is folklore knowledge as well as the experience of the perceptive physician that people may fall ill and die after the death of or separation from important family members. Grief, the normal response to a loss, is a process having both psychologic and physiologic aspects. Freud has pointed out the reparative and reconstructive aspects of grief as a means of overcoming a loss.[26] As many observers have noted, the patient with ulcerative colitis is often one who has failed to accomplish the work of grief, who has achieved no successful psychologic adjustment to the loss. It is suggested that this provokes a complex psychophysiologic state, a psychologic representation of which is the affect, and a somatic aspect of which is some process or processes eventuating in the tissue derangement.

The phenomena just described would be very general ones and might also, in other individuals, lead to other kinds of tissue derangements. We have observed similar settings for some cases of arthritis, asthma, dermatitis, malignant phase of hypertension, carcinoma, leukemia, Hodgkin's disease, congestive heart failure, to mention only a few.[24,32a] Why is the colon the affected site in these patients? (Actually, of course, the colon is not the only site.) Is there evidence for any kind of primary defect, in the colon, developmental or acquired in foetal life or early infancy? Evidence on this point is very sparse. The rare occurrence of ulcerative colitis in the newborn and very young infant speaks in favor of such an idea.[4] The incompleteness of the information on bowel function in the infancy of these patients has been noted but it is fairly well established that some kind of bowel dysfunction, usually constipation, long antedates the colitis. This, however, cannot be taken as evidence one way or the other for some primary defect in bowel wall and hence this remains an important subject for further research. If such defects exist, developmental or acquired early in infancy, it may be assumed that they contribute to the localization of the disorder in the bowel as well as to total personality development. The biologic characteristics of the body and its parts must be involved in the adaptive and developmental maturation of the individual and therefore also in the psychologic expressions thereof. In such an instance we would assume that the bowel would become specially invested emotionally and would more likely become an organ through which both pleasure and aggression might be expressed. Further, these processes would be implicated in the transaction between mother and child.

Since we cannot establish at this time whether

or not the bowel of the future ulcerative colitis patient is biologically distinctive, so to speak, I must leave this as an open question, which may be included or not in the formulation. What seems less uncertain is that the mother-child symbiosis is distinctive, and herein may lie factors which will determine the specific psychologic vulnerability of the individual and may contribute to the predilection for bowel trouble and headache as well. Present knowledge does not permit us to spell out details and, indeed, I believe the microscopic scrutiny of this relationship is the next required step in the psychologic elucidation of ulcerative colitis. It is also difficult to write about, because "mother-child symbiosis" is a transactional concept; it concerns the transactions whereby mother and child mutually relate and affect each other and it becomes misleading to try to describe mother and then child or vice versa.* The mother attempts to gratify certain needs through her child and may be frustrated and react in some way when the child fails to fulfil the need. The child, on the other hand, has certain basic needs, indeed needs which go to the very root of survival, which can only be achieved in the relation with mother or mother substitute. By virtue of the mother's behavior and character structure and/or by virtue of the inborn endowment of the child, its capacity for adjustment, these children grow up with serious defects in ego function. Benedek has pointed out how the child, in order to reduce the danger of separations, incorporates mother's conflicts, thereby adapting to mother's conflictful behavior.[3a] They may then remain permanently dependent on mother or on a limited number of substitutes, without whom they are literally helpless, since they cannot function in certain ways, having never successfully achieved independent means to do so. Elsewhere I have introduced the concept of "surrogate ego" functions to refer to these processes.[25b] Herein lies the overwhelming trauma of separation and the "curative" effect of a certain kind of doctor-patient relationship. I would list some of the important qualities of mother and of child which are implicated in this development as follows:† (1) The mother has an unresolved involvement with her own mother, which is often transferred to this one child. The details of this require further examination. (2) For a variety of reasons the mother's relation to the child is a "conditional" one, meaning that it may be relatively warm and succoring only when the child's behavior does not mobilize anxiety or guilt in mother. Transactionally, some of the child's intrinsic behavioral patterns, such

* Transaction is defined in Webster's New International Dictionary (1935) as, "An action or activity involving two parties or two things mutually affecting or reciprocally influencing one another." Dewey and Bentley[17a] have pointed out that man's organization and presentation of inquiry into natural processes has shown three successive levels of development. The first views of nature were *selfactional*, where things were viewed as acting under their own power. This corresponds to the magical, religious, animistic, or vitalistic concepts of the past centuries. Then with Galileo, Descartes and Newton there came into use *interactional* concepts, in which thing is balanced against thing in causal interconnection. This corresponds to the mechanistic, linear, cause-and-effect, stimulus-response concepts that have furnished the dominant pattern of scientific procedure, especially in medicine, up to the present. This is still a useful approach, under certain well defined conditions, but has imposed serious limitations on our understanding of natural processes. The transactional approach is ushered in by Einstein's field theory, which brought time and space into consideration and prepared the scene for Newton's unalterable particles to go the way of time and space. In the *transactional* concept, one observes processes, the "thing" in action, where the "thing" and the "process" are not separable one from the other. Thus in the case of organism and environment, *interaction* assumes organism and its environmental objects to be present as substantially separate existences or forms of existence, prior to their entry into joint investigation. *Transaction*, on the other hand, requires the acceptance of organisms and environment as a common system, and assumes that no preknowledge of either one alone as adequate; the organism is observed in process with environment. These concepts are now being developed in terms of open systems, dynamic steady states, feed-back mechanisms, and multifactorial concepts. It replaces the linear with the spiral, meaning that no system is ever again exactly the same as it was before. The patient is never "restored" to the same state of health that existed before he became ill; it is a different state. Every human relationship changes all participants. Health and disease must be understood in transactional terms.[23]

† Again I must emphasize the transactional aspects, the mutual feedback, as well as call attention to quantitative and qualitative differences. Some children are more vulnerable, some mothers more "pathogenic"; some children are more "pathogenic" to their mothers, with disastrous feedback; some families find themselves, through circumstances outside their control, in life situations which accentuate these problems. Otherwise we would be unable to account for the first attack of colitis occurring in childhood as well as in old age; colitis occurring in the person who barely gets by and the person who made a passably good adjustment before falling ill; the occurrence of colitis in one child but not in the siblings. A variety of factors, biologic, psychologic and social must come together before the colitis begins.

as feeding, bowel activity, motor activity, over which the baby has limited or no control, may be among the behavioral processes which evoke maternal anxiety, guilt or shame. Since these are operative from birth on, such tensions between mother and infant could contribute to the oral fixations so prominent in these patients. It is in this area particularly where biologically determined needs, as may be associated with some bowel defect, may contribute significantly to the symbiotic relation. (3) These mothers require a striking measure of control over the motility of their children or the children require control and succeed in enlisting it. This is expressed in the control over intake, motor activity, bowel movements and emotional expression which so often characterizes mother and child. Here again one sees mutual provocations, gratifications and resultant guilt. At this level of object relationship and ego development, fixation at and/or regression to the anal level of psychosexual functioning is mutually stimulated. (4) These children may have a defect in their autonomous capacity to relate to objects. More information is necessary on the development of very early relationships with people other than the mother. These children may also have a defective capacity to develop an independent ego, contributing to the need to continue to utilize others as "external" egos. In this and the preceding point I infer the possible existence of biologic defects as well as specific psychologic stresses from the environment. If such defects exist, however, they differ in degree, if not in kind, from the defects which lead to childhood psychoses.[59a] For the most part the reality testing function of these patients is not so seriously impaired. It is suggested that the difference lies in the fact that the colitis patient was better able to establish and maintain a symbiotic relationship than the psychotic child, but that this particular relationship forever largely determined and circumscribed to a high degree the nature of all other relationships. In terms of ego development this would not lead to as great damage to reality testing functions as occurs when no object relationship is established in the first year or so of life. But it would lead the individual extremely vulnerable to separation, as indeed these people are. (5) The psychosexual development of these individuals is arrested by virtue of the persistence of the symbiotic relationship, the need for "external" ego support. I have already mentioned some factors contributing to oral and anal fixations. A biologic defect ("organ weakness") may also contribute to these limitations. In any event, by virtue of the indispensibility of the key object (usually mother) as external ego, the oedipus complex cannot be resolved and mature sexuality is not achieved.

In this formulation, then, ulcerative colitis develops in particular individuals under specific circumstances. The tissue reaction, which forms the basis of the colitis, develops only when other adaptive processes fail, and the significant object relationship is threatened or actually interrupted. The specific factors that go into the development of this relationship will help to determine the kinds of circumstances and the settings in which this takes place. Biologic and psychologic developmental factors will help to determine the bowel as the site of the tissue breakdown. As long as an object relationship is maintained, other pathologic processes may become manifest, but not colitis. Thus the pathologic character traits constitute means for maintaining the key relationship and satisfying needs within that framework. Other neurotic, psychotic or psychosomatic symptoms (e.g. headache) develop during conflict situations within the framework of this relationship, where the relationship is not seriously threatened. Headaches, for example, develop when the patient takes a stand, expresses aggression, but maintains control. Conscious or unconscious guilt is associated with the headache, but not helplessness.[21] Elucidation of the specific aspects of the object relationship constitutes a most important problem for further research.

In respect to the pathogenesis of the tissue process itself, I can only speculate. I have already indicated my belief that this is a non-specific process, associated with the separation reaction and having no primary psychologic meaning. I suggest that when separation is not or cannot be dealt with by psychologic mechanisms (as in normal grief as well as in some types of neurotic or psychotic processes) physiologic changes are initiated in the body which interfere with or disrupt other adaptive or integrative processes, permitting various types of tissue breakdown, disturbances in local tissue growth, invasion by viruses or bacteria, etc. The nature of these processes remains unknown. Reichsman and I recently have observed in an infant with a gastric fistula a profound alteration in responsivity to histamine during object loss.[25a] This may

be indicative of some biochemical change characteristic of this state.* One possibility in ulcerative colitis is that these as yet unidentified changes may alter relationships in the colon so that it responds to its own flora as to pathogens. Another possibility is that the vascular system is particularly affected by these processes, perhaps becoming reactive to chemical substances elaborated as distant sites, in the tissues, or products of bacterial activity.

Such a formulation does not necessarily exclude the contribution of other mechanisms that have been proposed in other formulations. Thus the gastrocolic reflex[72,73] or the activation of eliminative patterns[1] would both be consistent with the psychodynamics of these patients and might add to the strain on colon. The failure of psychosexual maturation in these individuals might well involve erotization of the colonic mucosa, meaning that the colon becomes the site of physiologic changes, tumescent in character.[25,45,46,64] Beginning with mouth and with sucking, engorgement of mucous membrane and pleasurable sensations are both in the service of pleasure and of object relations. Such a regressive perversion of colonic function might be activated in situations when more advanced levels of object relation are threatened. This again might contribute to the final bowel change. And finally with motility in relationship to external world and objects markedly reduced, with the profound regression that accompanies this state, the turning inward of aggression may be associated with internal bodily changes, including changes in the colon. All of these are psychologic processes which may be expected to follow upon the traumatic separation, but whether they have physiologic aspects which specifically contribute to the colitis cannot be established by psychologic means alone. But we must avoid the error of assuming that the discovery of evidence favoring one mechanism necessarily means that other mechanisms are not also operative and perhaps contributing to the full development of the pathologic process. Indeed, there is every reason to believe that a chain of events results in the final pathologic derangement.

* That we should have encountered some process involving histamine is especially interesting since Feldberg has raised the question whether histamine release represents the first reaction of the mucosa to any form of injury. Also, the intestinal bacteria form histamine from histidine, and many food substances contain histadine.[25c]

SUMMARY

1. The psychologic data in thirty-nine patients with ulcerative colitis have been summarized and published reports on more than 700 patients have been reviewed.

2. Among these patients there was found with impressive consistency (*a*) defects in personality structure long antedating the onset of colitis, (*b*) a characteristic type of dependent and restricted relationship with people, (*c*) consistent psychopathology in the mothers, and (*d*) failure to achieve full heterosexual development.

3. The onset and relapses of the disease were found to occur in settings which represented to the patient real, threatened or fantasied interruptions of key relationships, but the disease developed only when the corresponding affect was helplessness, despair, hopelessness, etc.

4. In conflict situations which were not responded to with such effect, other neurotic, psychotic or psychosomatic (notably headache) reactions were observed.

5. Various psychosomatic hypotheses are critically reviewed.

6. A modified formulation is offered which (*a*) stresses the significance of the mother-child symbiosis in determining the particular personality development and vulnerability to separation, (*b*) relates the tissue reaction of ulcerative colitis to biologic changes occurring consequent to traumatic separations, (*c*) and attempts to account for the choice of organ (colon) on the basis of constitutional and experiential factors in the mother-child transaction.

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Seminars on Carbohydrate Metabolism

Current Views on the Mechanisms of Insulin Action*

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THIS paper will try to develop a picture of the current concepts of the problem of the action of insulin upon intermediary metabolism. The theoretic background necessary for a reasonable understanding of the problem will be discussed. Then the experimental evidence which at this time seems most significant will be presented and evaluated. Necessarily, the great mass of literature at hand makes selection imperative, and much data will be omitted which some may think of prime importance.

The problem of the action of insulin may be said to have begun with the demonstration of Minkowski and Von Mehring that a state closely resembling diabetes mellitus could be produced in the dog by surgical removal of the pancreas. These experiments demonstrated beyond doubt that the pattern of defective metabolism associated with diabetes was due to the absence of some humoral principle elaborated by the pancreas. The discovery of insulin by Banting and Best followed in 1922. This initial phase in the history of the problem of insulin action did not end here but rather with the demonstration by Houssay and Biasotte (1931)[19] that experimental diabetes could be ameliorated by the simultaneous removal of the anterior pituitary. The demonstration by Long and Lukens (1936)[28] of similar amelioration by simultaneous adrenalectomy completed the picture: The metabolic patterns which result from the activity of tissue enzyme systems are under the control of the complex interplay of a series of hormones whose balance or imbalance produces normal and beneficial homeostasis or profound and often fatal aberrations.

The picture which emerged from these early studies is greatly oversimplified and is a familiar one. There is in diabetes an accumulation of glucose in the body giving hyperglycemia and glycosuria. A decreased storage ability results in lowered glycogen content of muscle and liver. The low respiratory quotient is attributed to decreased or absent oxidation of carbohydrate. The disturbed fat metabolism is manifested by marked loss of body fat and fatal ketosis. An increase of protein catabolism results in a loss of body tissue and increased nitrogen output.

In this early period of study on the problem of the action of insulin experiments on the whole were limited to studies of total metabolism involving measurements of blood sugar, shifts of carbohydrate stores from one organ to another, respiratory quotients, change of total protein metabolism, effect of altered diabetic state upon ketosis, and the like. Experiments were mostly confined to the intact animal and were concerned with measurements of glycogen, lactic acid, ketones, and so on. The ratio of dextrose to nitrogen in the urine (D:N), for example, was a favored method for evaluation of the severity of the diabetes. It is interesting to note that Lusk in his Harvey Lecture in 1904 on "Metabolism in Diabetes Mellitus" makes no reference whatever to "intermediary metabolism."

This period was dominated by what might be called the monistic view: namely, that the metabolic defect associated with diabetes was due to the lack of one hormone. Further, in the total diabetic there was 100 per cent disability. Two main theories were proposed to explain this. Reduced to its elements, these views are expressed with great brevity in Table 1. Underutilization meant that there was complete inability of the organism to oxidize carbo-

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hydrate. The metabolic requirements were met entirely by fat and by that part of protein which was not glucogenic. The respiratory quotient, of 0.7, was that of the burning of pure fat. In the fasted diabetic, (D:N) expressed the ratio of the dextrose to nitrogen found in the urine. In

TABLE 1
UNDERUTILIZATION VERSUS OVERPRODUCTION

Respiratory quotient	0.7
D:N ratio	3.5
Fat to carbohydrate	C_2 to C_4 (?)

the fed animal this ratio was corrected for the ingested food, including that portion of the protein and fat which was assumed to be convertible to carbohydrate. The value commonly used is 3.0 to 3.5, based upon limited experiments with dogs or a few human cases assumed to be totally diabetic. This value was explainable on the assumption that about 50 to 60 per cent of the amino acids of protein were converted to glucose and were excreted unused. Fat was never a source of carbohydrate.

The opposing view held that no impairment in the ability of the organism to oxidize carbohydrate resulted. Hyperglycemia was regarded as a compensatory mechanism which enabled the diabetic to oxidize carbohydrate. But overcompensation resulted in glycosuria. The extra glucose necessary for this hyperglycemia was derived not only from protein but from fatty acids. (The glycerol portion of the fat was always calculated with the carbohydrate.) The precise reactions by which fatty acids were converted into carbohydrate were never clearly explained.

Rumblings of this controversy still continue but the introduction of tracers in metabolic studies has settled it. The kernel of the situation is expressed in the table by C_2 to C_4(?). It has been abundantly shown that all fat metabolism goes through the formation of the two-carbon compounds—acetyl-coenzyme A. This condenses with four-carbon compounds (oxalacetic acid) to enter the Krebs cycle for further conversion or oxidation. Any member of the Krebs cycle may be incorporated into protein, fat or carbohydrate. Hence it is possible, as has been shown experimentally by tracer studies, that carbon atoms derived originally from fatty acids may be found in carbohydrates. But the important distinction is that the four-carbon compounds necessary for combination with the two-carbon compounds always come from preexisting carbohydrates and never from fat. Hence a net new formation of carbohydrate from fatty acids does not occur.

We can say the same thing in another way: An obligatory step in the formation of carbohydrate from fat would be the condensation of two C_2-compounds (monocarboxylic acid) to a C_4-compound (dicarboxylic acid). But this so-called Thunberg reaction has never been demonstrated to occur in mammalian tissue.

The demonstration by Houssay and Biasotte (1931)[19] and by Long and Lukens (1936)[28] that the diabetic state could be ameliorated by concomitant removal of the pituitary or adrenals initiated a new phase in the problem of the action of insulin. Carbohydrate metabolism and concomitant fat and protein metabolism were obviously under hormonal control involving at least three enzyme systems. Furthermore, the monistic theories suggesting that the diabetic organism has only one metabolic defect, either an inability to oxidize glucose or a gross overproduction of glucose from fat or protein, became untenable. It was obvious that all three types of metabolism were under multiple hormonal control.

Simultaneous with these interesting developments in the field of diabetes a new field began to dominate thought and experiments in metabolic studies. This was the spectacular development of enzyme chemistry in the first half of the century. Buchner first demonstrated the catalytic activity of an enzyme system dissociated from the living cell. There followed from laboratories all over the world demonstrations of the properties of enzyme systems derived from living tissues. Many of these enzyme systems were isolated in pure form and were shown to catalyze, with high specificity, single chemical reactions. Many were crystallized and the cofactors necessary for their action were isolated and identified. The innumerable chemical reactions involved in the total metabolism of food stuffs were demonstrated and, although knowledge was still incomplete, patterns of chemical reactions were mapped which described these metabolic processes in detail. Thus the study of intermediary metabolism, as distinguished from total metabolism, became dominant. The experimental use of surviving tissues, such as heart-lung preparations, eviscerated animals, perfused isolated organs, surviving tissue slices or homogenates, and tissue extracts became widely used as new experimental tools.

This new approach rapidly brought insight

into the problem of the action of insulin. For the sake of simplicity we may discuss this in two ways. For want of better terms we may call the first the physiologic approach and the second the molecular consideration. The physiologic approach endeavors to study an isolated chemical reaction occurring in the course of intermediary metabolism of carbohydrates, proteins and fats to determine whether it is inhibited or accelerated by the presence or absence of insulin or insulin antagonists. Thus the "biochemical lesions," as they have come to be known, which occur in the diabetic may be written in the form of chemical reactions as aberrations from normality. Most of the reports in the literature are concerned with this type of study. In opposition to this, the molecular approach has a different aim. For example, we know that enzymes influence reactions of foodstuffs in such a way as to bring about their transformation, final oxidation or synthesis more rapidly than would be the case if the catalytic action of enzyme systems was not available. The molecular mechanisms by which this is brought about are little understood. Molecules are known to exist in different states of reactivity and the presumption is that enzymes bring about a higher concentration of the reactive forms so that the "energy hump" which hinders the desired reaction may be overcome. However, one mechanism has been well established, namely, the combination of substrates with enzymes according to the Michaelis-Menton concept (vide Clark, 1952[8]). Presumably such combination is a prerequisite for enzymatic action. What is the relation of hormones, particularly insulin, to such an enzyme-substrate complex? Little is known of this aspect of hormonal action except perhaps that the binding of insulin to tissue (vide infra) may be a necessary requisite for hormonal action. Possibly hormones change configurational patterns of enzymes in such a way that substrate combination becomes radically altered. The precise mechanism by which hormones interact with the enzymes of the tissue remains to be elucidated and, until this has been done, there can be no fundamental concept of the nature of diseases associated with endocrine imbalance.

These preliminary remarks about the general aspects of intermediary metabolism make a consideration of the possible biochemical defects due to a deficiency of insulin or to an excess of contrainsulin factors more intelligible. The possible sites of insulin action which are most prominent in current discussions of the biochemistry of diabetes are: (1) increase of cell permeability or transfer of glucose across cell barriers to enzymatic sites; (2) acceleration of the hexokinase reaction; (3) increase of high-energy phosphate formation, and (4) effect on

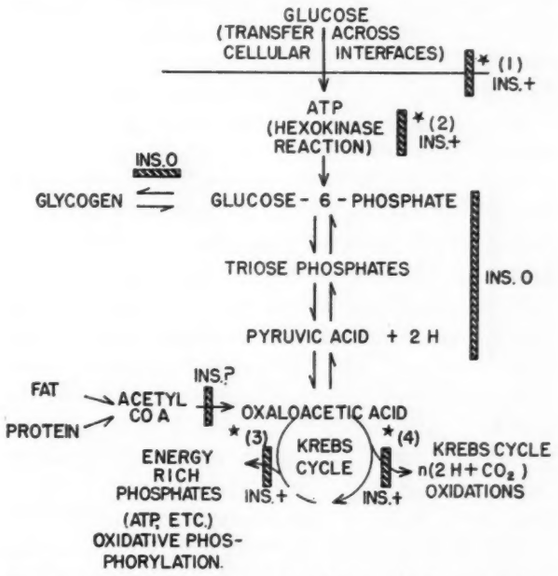


FIG. 1. Current schema of glycolytic and Krebs cycles. Possible "metabolic defects" associated with insulin deficiency are indicated by hatched blocks: (1) glucose transfer, (2) hexokinase reaction, (3) oxidative phosphorylation, and (4) oxidative reactions in Krebs cycle.

oxidative reactions of the Krebs cycle. A consideration of these and a knowledge of the glycolytic cycle and its relation to the Krebs cycle (outlined in the schema shown in Fig. 1) form a framework about which the problem of the action of insulin may be discussed. A preliminary consideration of the nature of these defects will be given first, followed by a more detailed presentation of the experimental evidence upon which the concepts are based.

The first conceivable biochemical lesion concerns itself with the permeation of glucose through cellular barriers to sites of enzymatic action. The forces which hinder or accelerate the access of glucose to enzyme systems may be of a physical or a chemical character. At present there is no certain way of differentiating the two so that it is best to call the mechanism concerned with the permeation of glucose to enzyme sites a transfer mechanism. It is important to realize that the cell is composed of many subcellular structures such as mitochondria, microsomes, nuclei, and so on. Each of these

cell-particulates is known to contain systems of enzymes concerned with carbohydrate metabolism. In turn, each of these systems is separated by a cellular barrier from its surroundings. These considerations naturally render the problem of the action of insulin upon transfer very complex. We can say no more at present but that there is evidence indicating that the transfer of glucose (and other sugars) to enzyme sites appears to be under hormonal control.

The second possible biochemical lesion in insulin lack is related to the activation of glucose. It is now well established that in practically all mammalian organisms glucose is prepared for further metabolism by the formation of glucose-6-phosphate. Glucose metabolism without phosphorylation, if it occurs at all, is so exceptional that it may be dismissed from further consideration. The formation of glucose-6-phosphate does not occur unless catalyzed by the enzyme, glucohexokinase, which is present in practically all mammalian cells. The reaction (which is essentially irreversible) is:

Glucose + ATP = glucose-6-phosphate + ADP.

The third possible diabetic defect involves the production and storage of high-energy phosphate compounds such as ATP, creatine phosphate or similar compounds. Many reactions depend upon the availability of ATP, for example glucose-6-phosphate formation, synthesis of fatty acids, certain oxidative reactions, synthesis of protein or possibly the penetration of glucose through cellular barriers. It is therefore natural to consider the possibility that defects in the production of high-energy phosphates might be involved in the diabetic state and, indeed, there is much evidence to support this point of view.

The fourth and last diabetic lesion which is considered in the literature is concerned with defects in oxidative reactions, particularly of derivatives of glucose. These oxidative reactions appear to be limited to reactions involving the Krebs cycle. The existence of this type of diabetic defect is not too convincingly supported by evidence in the literature and there is therefore a tendency to neglect it in discussions of insulin action.

Following the initiation of the metabolism of glucose by phosphorylation, glycolysis continues by a conversion of the monophosphate to diphosphate and then by a split into two triose molecules. These 3-carbon compounds form pyruvic acid, the link which joins the glycolytic cycle to the Krebs cycle. The linkage of the glycolytic cycle with the Krebs cycle is by way of a condensation of pyruvic acid with oxalacetic acid. One oxidative step occurs with the elimination of one molecule of CO_2 and the formation of citric acid, the first member of the Krebs dicarboxylic acid cycle. Provision is made in the glycolytic cycle for the storage of carbohydrate. Glucose-6-phosphate is converted into glucose-1-phosphate (by phosphoglucomutase) which in turn is converted to glycogen (catalyzed by phosphorylase). All the reactions of the glycolytic cycle from pyruvic acid to glycogen are reversible. This means that either glucose or pyruvic acid or any of the intermediaries are capable of forming glycogen. The hexokinase reaction is irreversible and glucose can only be regenerated from glucose-6-phosphate by the splitting off of inorganic phosphate catalyzed by phosphatase.

HEXOSE-MONOPHOSPHATE-SHUNT

Much recent evidence in the literature indicates that a pathway of metabolism of glucose, other than through the glycolytic cycle, exists. This involves the oxidation of hexose-monophosphate to phosphohexonic acid. Loss of CO_2 by decarboxylation reduces this compound to a 5-carbon compound which is then split into 2- and 3-carbon compounds. There is no evidence that this so-called hexose-monophosphate-shunt is involved in the insulin problem. Therefore, it will be dismissed from further consideration.

The oxidation occurring in the Krebs cycle are always accompanied by decarboxylations yielding CO_2. In this way the three carbons of the pyruvic acids are oxidized and the original 4-carbon oxalacetic acid is regenerated. The energy yielded by these oxidations forms the high-energy phosphate bonds of ATP which may be retained as such or stored as creatine phosphate. This stored chemical energy is available for a whole series of endergonic reactions (requiring input of energy) such as synthesis of fat, synthesis of protein, acetylation, and so on. It is to be noted that the initial activation of phosphorylation of glucose is one of these reactions. Fat and protein enter into the metabolic schema by the formation of 2-carbon compounds which when combined with coenzyme A enter the Krebs cycle via oxalacetic acid.

Before examining evidence for the hypotheses of the specific action of insulin, some of the recent data bearing on the general question of

the action of insulin upon intermediary metabolism will be discussed. Such a brief review of the recent literature must necessarily be selective and illustrative rather than complete.

With respect to carbohydrate storage as glycogen in liver and muscle, much conflicting evidence is present in the literature as to the role of insulin. Concomitant action of adrenalin and transfer of carbohydrate from liver to muscle complicates these experiments. Bouckaert and deDuve (1947)[2] report experiments which they interpret to mean that insulin is of major significance in the accumulation of glycogen in the liver. They maintain the blood sugar in the experimental animal (dog) at high levels by measured infusion of glucose. The amount of glucose necessary to maintain these levels was assumed to represent glycogen storage. In the absence of insulin only small amounts of glucose were removed from the blood stream but if maximal doses of insulin were given to the preparation glucose storage resulted. The data summarized in Table II show that the eviscerated and hepatectomized preparation retained about the same amount of glucose, but the dog with liver intact required about five times as much injected glucose to maintain constant blood levels. Most of this excess glucose represents extra storage as glycogen in the liver under the influence of insulin.

TABLE II

STORAGE OF GLYCOGEN IN LIVER IN DOG INJECTED WITH INSULIN: STORAGE MEASURED BY AMOUNT OF INJECTED GLUCOSE REQUIRED TO MAINTAIN CONSTANT BLOOD LEVEL[2]

	Gm./Kg./80 Min.	
	Mean	SEM
Control (liver intact)	2.10	± 0.24
Hepatectomy	0.40	± 0.12
Evisceration	0.40	± 0.22
Intact without insulin		± 0

Lang, Goldstein and Levine (1954)[27] objected to this interpretation of Bouckaert and deDuve. They reported experimental observations which they interpret to mean that, following hepatectomy, there is decreased peripheral glucose uptake. This means, they concluded, that there is a humoral factor of hepatic origin which stimulates peripheral glucose utilization. The experiments of Bouckaert and deDuve do not necessarily mean, therefore, that insulin has a direct hepatic action in glycogen storage but might indicate the action of the humoral of the liver on peripheral storage. The difficulty in demonstrating direct insulin effect upon the metabolism of liver has recently been clarified by interesting experiments reported by Renold, Hastings, Nesbett and Ashmore (1955).[33] They report a striking difference between the times of response of the rat diaphragm and liver slices to insulin. In the alloxanized rat the diaphragm responds immediately to the action of injected insulin by increased glucose uptake, glycogen synthesis and CO_2 production. In contrast, hepatic carbohydrate metabolism, as measured by glucose uptake, glycogen synthesis from glucose or pyruvate and CO_2 production, shows only minimal effect of insulin six hours after beginning of administration. Complete restoration to normal values does not occur until twenty-four to forty-eight hours after insulin treatment has begun. In this connection a puzzling difference between the action of insulin upon the carbohydrate and fat metabolism of liver slices in the medium is to be noted. Effects upon the incorporation of labeled acetate into higher fatty acids is easy to demonstrate (Brady and Gurin, 1950;[3] Haugaard and Stadie, 1953[18]) but effects upon carbohydrate metabolism (increased glycogen synthesis, increased CO_2 production) cannot be demonstrated. The recent experiment of Renold et al. (1955)[33] might indicate a possible solution of this difficulty.

The evidence that insulin enhances glycogen storage in muscle is abundant and need not be cited in detail. The diaphragm is used extensively for metabolic studies. The rat is easily altered so that experiments may be performed under a variety of metabolic and endocrine conditions. For these reasons rat diaphragm is ideal for *in vitro* studies. Gemmill (1940)[12] first showed that the rat diaphragm survived excellently *in vitro*, utilized glucose from the medium and responded to insulin by utilizing more sugar and synthesizing more glycogen. Mere addition of insulin to the glucose-containing medium increases glycogen storage. In the alloxan-diabetic rat, glycogen storage is sharply decreased and insulin in the medium increases the glycogen synthesis but does not increase it entirely to within normal limits.

Is insulin necessary for glycogen storage? The answer to this was obtained by experiments of Lukens (1934).[29] He examined the breakdown

and resynthesis of muscle glycogen in depancreatized cats at various times. The same level of muscle glycogen was obtained in the depancreatized cat as in the normal cat but the time required to accomplish this was longer.

The effect of insulin upon carbohydrate metabolism in the normal rabbit is well shown by some experiments of Wick et al. (1951)[51] which are summarized in Table III. They used isotopic glucose which was injected into the blood stream of the eviscerated preparation. Subsequently the carcass was analyzed for protein, fat and glycogen for the determination of radioactivity. From these data, as well as from the isotopic carbon recovered in the respiratory CO_2, the glucose equivalents oxidized and the glucose converted to glycogen, protein or fat could be calculated. Compared to the controls, insulin brought about marked increases in all categories: The oxidation of the glucose was increased about fourfold, glycogen storage about fivefold, and incorporation into protein and fatty acids six- and thirteen-fold, respectively. This experiment shows quite well the effect of insulin upon the general metabolic picture.

TABLE III

DETERMINATION OF THE EFFECT OF INSULIN ON GLUCOSE METABOLISM IN EVISCERATED RABBITS USING ISOTOPIC GLUCOSE[51]

	Mean of 4 Mg. Glucose Equivalents	
	Control	Insulin
CO_2	650	2500
Glycogen	130	700
Protein	110	700
Fatty acids	10	130

What about carbohydrate metabolism in the intact diabetic animal? In the early literature, and even up to somewhat recent times, there was considerable confusion in the literature with respect to this situation. Opposing views maintained, on the one extreme, that the total diabetic was totally unable to oxidize glucose. The other extreme view maintained that there was no impairment of glucose oxidation in the diabetic. Some recent experiments by Stetten, Welt, Ingle and Morley (1951)[49] and also by Feller, Chaikoff, Strisower and Searle (1951)[10] using isotopic glucose in alloxanized rats and depancreatized dogs have clarified this situation. The summarized data of Stetten et al. are shown in Table IV.

Normal, alloxan-diabetic and phlorhizinized rats were used in these experiments. These rats under membutal anesthesia were arranged for continuous injection of isotopic glucose, collection of urine and expired CO_2. The injection of C^{14}-labeled glucose was at a constant rate and sufficient to maintain a constant level of glycosuria during the experiment. The time period was up to twelve hours and during the later part of this period not only was the glucose excretion constant in rate but the specific activity of the glucose was also constant. Under these circumstances it was possible to calculate the rate of production of glucose from non-glucose sources. In addition, the determination of radioactivity of expired CO_2 permitted an estimation of the glucose oxidized. The summarized data (Table IV) show: (1) the rate of production of glucose from non-glucose sources and (2) the glucose oxidized to CO_2. The authors conclude "that in the normal rat, the rates of glucose production and oxidation are approximately of the same order. In the phlorhizinized animal, a marked impairment in glucose oxidation is apparent, whereas the rate of glucose formation is unaltered." In the alloxanized diabetic rat "there appears to be a small increase in the rate of glucose production, although statistically this may not be significant. There is little question, however, that a decrease in the rate of oxidation of glucose occurred in this condition, the elevation in glucose concentration accompanying the disease." Feller et al. (1951)[10] reported results on the depancreatized dog which are in substantial agreement with the conclusions of Stetten and his colleagues.

TABLE IV

GLUCOSE UTILIZATION IN ALLOXANIZED RATS[49]

Glucose	Normal (mg./100 gm. rat/hr.)	Phlorhizinized	Alloxanized
Produced	15.0	14.0	21.0
Oxidized to CO_2	11.5	2.6	4.5

The following conclusions may be regarded as being reasonably well established by several groups of workers using various types of experimental animals: (1) Glycogen synthesis from

glucose by liver and muscle persists in the absence of insulin but the rate of formation is diminished. (2) Compared to the normal animal, there appears to be an overproduction of glucose from protein, although the evidence is somewhat conflicting on this point. Net new formation of glucose from fat has not been demonstrated. (3) There can be little doubt that insulin markedly stimulates glycogen synthesis and carbohydrate oxidation in the normal as well as in the diabetic animal. (4) In the alloxanized or depancreatized rat, rabbit and dog, there is significantly diminished oxidation of glucose, but oxidation is not completely abolished.

It is possible that differences within the species may obscure interpretation of experimental results so that judgment must still be reserved. For example, some of the questions have not yet been adequately tested in the depancreatized cat.

EFFECT OF INSULIN ON FAT METABOLISM IN DIABETES

Disturbances of fat metabolism in diabetes have long been known. Early concepts held that the complete diabetic was dependent entirely upon the 2-carbon compounds derived from fat for his energy requirements. The ketones known to be derived from fat were not burned and were excreted as such. This view is no longer tenable.

The concept now accepted is illustrated by the experiments shown in Figure 2. The ability of the liver of the diabetic to synthesize fat is impaired. In addition, large amounts of fat are broken down into ketone bodies by beta oxidation. Certain 2-carbon compounds are formed which, by random redistribution, combine to form 4-carbon ketone bodies. Most of these ketones formed by the liver of the diabetic animal are oxidized completely in the peripheral tissues and are therefore an important source of energy for the animal. A relatively small amount is excreted in the urine. This is well illustrated by the data shown in the illustration. Diabetic cats well treated with insulin no longer produce these excessive amounts of ketone bodies, and slices from the liver of Houssay cats produce essentially none when equilibrated *in vitro*.

The deficiency with respect to fatty acid synthesis, demonstrated by the experiments of Stetten and Klein (1946),[48] are summarized in Table v. These authors determined the rate of synthesis of fatty acids in the normal and in the diabetic rat by means of heavy-water ingestion. From the deuterium incorporated into the fatty acids it is possible to calculate comparative rates of formation of fatty acids from different substrates such as glucose or acetate. The data in

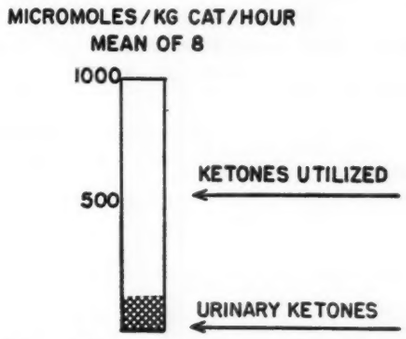


FIG. 2. Uncontrolled fatty acid metabolism of diabetic cat liver (depancreatized cats). Ketone formation by liver slices from fatty acids accounts for almost all of the oxygen uptake; most of the ketones formed are utilized by the muscles; liver slices from normal cats produce little or no ketones.[47]

Table v show that the ability of the liver of the diabetic rat to synthesize fatty acids and glucose is much less than in the normal rat. Furthermore, insulin in the normal animal increases fatty acid synthesis approximately five-fold whereas it has no significant effect in the diabetic. Deficiency of fat synthesis thus became established as a major metabolic defect of the diabetic. Stetten and Klein (1946)[48] did not conclude that this defect was a primary one in diabetes. Subsequent work by others makes it apparent that fat synthesis fails when there is inability, as in the diabetic or starved animal, for intermediaries of the glycolytic or Krebs cycle to be derived from glucose.

The inability of the liver of the diabetic to synthesize fatty acids from glucose, acetate and lactate has been well established by experiments with liver slices and labeled nutrilites. Typical evidence of this type is shown in Table vi which gives representative data from some experiments of Chernick and Chaikoff (1950).[6] The liver from alloxanized rats fails completely to incorporate the labeled glucose into fatty acids. Prolonged insulin treatment prior to sacrifice of the rat for the preparation of the liver slices is required for the restoration of fatty acid synthesis. It might be re-emphasized here, as referred to in the previous discussion of the

paper of Renold, Hastings, Nesbett and Ashmore (1955),[33] that, whereas the addition of insulin to normal rat liver slices results in increase of fatty acid synthesis of acetate, no such insulin effect has been demonstrated unequivocally by the mere addition of insulin to liver slices equilibrated *in vitro*. Prior treatment of some long duration is necessary to bring about such insulin effect.

TABLE V
LIPOGENESIS FROM GLUCOSE DETERMINED BY DEUTERIUM FEEDING[48]

	Deuterium in Fatty Acids (per cent of D in body water)	
	Liver	Carcass
Diabetic	2.7	1.2
Diabetic + insulin	1.4	1.1
Normal	6.6	0.8
Normal + insulin	26.1	2.3

TABLE VI
CONVERSION OF C^{14}-GLUCOSE TO FATTY ACIDS BY ALLOXANIZED RAT LIVER SLICES[6]

	Per cent C^{14}-Glucose per Gm. Liver as Fatty Acids
Untreated	0.00; 0.02
Insulin treated	0.37; 0.67; 0.50

RELATIONSHIP BETWEEN CARBOHYDRATE AND FAT METABOLISM

There are many experiments in the literature by Lehninger (1951)[25] and others which show that fatty acid metabolism by liver mitochondria can proceed in several directions depending upon the makeup of the system with respect to carbohydrate intermediaries. Thus the experimenter can arrange to have, within certain limits, fatty acid oxidation, fatty acid synthesis or ketone formation predominate. There are experiments on other tissues which show similar interrelations between fatty and carbohydrate metabolism and which have significance in current conceptions of insulin action.

Baker, Chaikoff and Schusdek (1952)[1] reported experiments bearing on this aspect of the insulin problem. (Table VII.) They measured the incorporation of labeled nutrilites into fatty acids by rat liver slices *in vitro*, using rats which had been on various diets for two or three days before the experiment. In the case of the normal rat, glucose or fructose in the prior diet made no difference in the fatty acid synthesis of lactate or acetate. The alloxanized rats, however, behaved differently. When glucose was the sugar fed the rat liver slices showed markedly diminished fat synthesis from lactate or acetate. In the case of fructose feeding, however, synthesizing ability was essentially that of normal. It is to be noted that these effects were obtained without insulin. Furthermore, the ability of the liver slice to oxidize glucose was not restored. It appears from these experiments that loss of lipogenesis by the liver of the diabetic is not a primary defect. It appears to be secondary to loss of ability to utilize glucose. Fructose can circumvent the difficulty and furnish products of glycolysis which, by their metabolism, furnish energy for the synthesis of fatty acids. These experiments have commonly been interpreted to mean that in diabetes the action of glucohexokinase is impaired so that glucose cannot be phosphorylated by the hexokinase reaction to enter into the glycolytic schema. On the other hand, fructohexokinase, which has been shown to exist as a separate enzyme distinct from glucohexokinase, is supposed to be unaffected in the diabetic. However, a close examination of the literature, for example, Renold, Hastings, Nesbett and Ashmore (1955),[33] demonstrates that the ability of alloxanized rat liver to metabolize fructose, while not abolished, is significantly lower than in normal rats. In view

TABLE VII
EFFECT OF DIET ON SYNTHESIS OF FATTY ACIDS BY RAT LIVER SLICES[1]

	Previous Diet	Per cent of Isotope Recovered in Fatty Acid/0.5 Gm. (mean of 4 to 5 rats)	
		Lactate	Acetate
Normal	Glucose	3.3	5.5
Normal	Fructose	5.1	7.7
Diabetic	Glucose	0.5	0.8
Diabetic	Fructose	3.0	3.5

of this finding it cannot be maintained that the defect in diabetes impeding the metabolism of glucose is completely non-operative in the case of fructose.

The dependence of fatty acid synthesis from lower fatty acids upon products of glycolysis has been well demonstrated by a number of workers: Brady and Gurin (1950),[4] and Shaw and Gurin (1953).[40] Brady and Gurin found that liver slices from fasted or diabetic animals cannot synthesize fatty acids from labeled acetate, in contrast to corresponding preparations from normal fed rats. Summarized data from the work of Shaw and Gurin are shown in Table VIII.

TABLE VIII
FATTY ACID SYNTHESIS BY EXTRACTS OF LIVERS OBTAINED FROM DEPANCREATIZED PIGEONS[40]

Liver Extract	Isotopic Acetate Synthesized into Higher Fatty Acids. Micromoles/10 Mg. of Fatty Acids
Normal pigeons	0.61
Diabetic pigeons	
Additions to medium	
No additions	0.1
Glycogen	1.0
Fructose-1-6-diphosphate	1.7
Glucose-6-phosphate	0.3*
Insulin	No effect

* Higher results were obtained in later experiments.

To overcome the difficulties of cell permeability and other problems pertaining to entrance of nutrilites into the cell, cell-free preparations of mitochondria from livers of depancreatized pigeons or alloxanized rats were used. These preparations retain active glycolytic properties and also perform all the oxidative reactions of the Krebs cycle. In the presence of compounds capable of glycolysis and oxidation by these mitochondrial suspensions, fatty acid synthesis occurs at a rate comparable to that of the intact liver slices. These compounds were hexose monophosphate, hexose diphosphate and glycogen. These authors also found that ATP and diphosphopyridine nucleotide are necessary for the synthesis. It must be remembered that intact slices from normal fed rats respond to insulin by incorporating more labeled acetate into fatty acids, in contrast to slices from fasted or diabetic rats which do not respond to insulin. These facts, together with the recent experiments of Haugaard and Stadie (1952),[17] indicate that oxidation of glycolytic products furnish the energy (presumably through the formation of ATP) to bring about the synthesis of fatty acids by liver. (Fig. 3.)

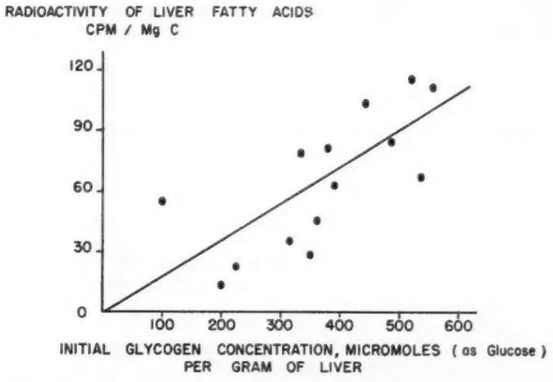


FIG. 3. Association of fatty acid synthesis and glycolysis. The initial liver glycogen was varied by antecedent feeding. The higher the initial value, the greater is the incorporation of isotopic acetate into fatty acids, thus indicating the need for glycolytic products for the synthesis.[17]

CONSIDERATION OF THEORIES OF METABOLIC DEFECTS ATTRIBUTABLE TO INSULIN DEFICIENCY

There are many papers in the literature which report experiments seeking to pinpoint a metabolic defect resulting from insulin deficiency or excess of contrainsulin factors. These have been numbered in the metabolic schema shown in Figure 1 and are: (1) the permeability or transfer hypothesis, (2) the glucohexokinase hypothesis, (3) the hypothesis implicating deficiencies of high-energy phosphate formation, and (4) failure of key oxidative reactions, particularly of the Krebs cycle. Space does not permit a detailed discussion of all the evidence available in this field. An attempt will be made to evaluate critical evidence in relation to the aforementioned hypotheses.

1. Permeability or Transfer Hypothesis. This postulates that, at cell surfaces or perhaps at cell-particulate interfaces which separate enzyme systems one from another, there are barriers (either of a physical or a chemical character) that control the entrance of metabolites to the sites of enzyme action. These barriers may be altered by imbalance of hormones such as insulin (alone or associated with pituitary or

adrenal factors) so that impairment of transfer is altered.

Representative data reported by Levine and his coworkers (1950),[26] who were the first to advocate the permeability or transfer theory, are shown in Figure 4. Eviscerated-nephrectomized

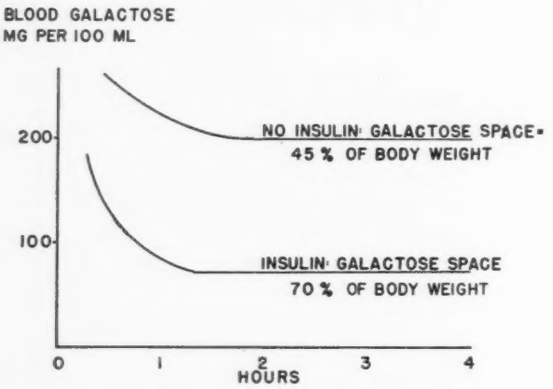
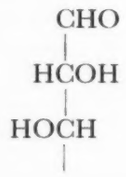


FIG. 4. Permeability theory of insulin action. A metabolically inert sugar (galactose) was injected into eviscerated-nephrectomized dogs and the blood galactose levels followed. Insulin injection markedly increased the "galactose space" indicating its action on "transfer of sugar" across cell barriers.[13]

animals were used into which were injected galactose intravenously. Within a comparatively short time after the injection blood galactose levels became constant, and a calculation of the volume of distribution of galactose could be calculated since, in the type of preparation used, galactose is not metabolized. Without insulin, as the illustration shows, the galactose space was approximately 45 per cent of the weight of the preparation. But following insulin injection this increased regularly to about 75 per cent, which represents body water. These results were interpreted by the authors to mean that there is a barrier which normally excludes glucose from the considerable portion of the body space but under the action of insulin this barrier is lifted. The mechanism by which insulin produces this effect is unknown. In order to avoid implications as to mechanisms, Levine et al. (1950)[26] advocated that the mechanism be termed a "transfer mechanism" rather than a "permeability mechanism." These authors performed similar experiments using a variety of sugars of different configurations. They found that some were "insulin-responsive" whereas others were "insulin-non-responsive." The insulin-responsive sugars had a common configuration in carbon 1, 2 and 3, namely:



Later Park (1953)[30] used isotopic glucose under appropriate conditions and showed that the injection of insulin was followed by an increase of "free" glucose in the heart, skeletal muscle and diaphragm of the rat:

Glucose in tissues

Extracellular distribution	No insulin
Distribution increased four- to fivefold	With insulin

Mirsky and his coworkers (1953)[15] performed similar experiments studying the rate of penetration of various sugars into the rat diaphragm *in vitro*. They also concluded that one action of insulin was to accelerate the entrance of certain sugars into muscle. Confirmatory evidence of the transfer hypothesis was reported by Ross (1951 and 1952).[35,36] Ross studied the rate of transfer of glucose across the blood-aqueous barrier in the eye of the normal alloxanized rabbit. He obtained his experimental results by maintaining the blood sugar of the rabbit at elevated levels by appropriate injection and then measuring the rate of increase of glucose concentration in samples of aqueous humor obtained from time to time from the anterior chamber. These data enabled him to calculate velocity constants expressing the rate of transfer of glucose across the barrier of the ciliary bodies. In contrast to the normal rabbit, the velocity constants of glucose transfer were significantly diminished in the alloxanized rabbit. Ross also found that under the action of injected insulin the rate of transfer of glucose across this cell barrier increased.

The evidence here presented seems impressive in indicating that insulin is concerned with the passage of glucose across cell boundaries. The manner in which this effect is achieved remains unknown and the precise significance of a possible decrease in permeation of glucose into tissues as a factor in diabetes mellitus remains to be determined. As will be discussed subsequently, the demonstration of insulin effects upon glucose transfer makes it difficult to evaluate certain evidence which has hitherto been cited to support the hexokinase theory of insulin action.

2. Hexokinase Theory of Insulin Action. Consideration of the metabolic schema shown in Figure 1 indicates that interference with the catalytic action of glucohexokinase results in diminished formation of glucose-6-phosphate. As a result, the entrance of glucose into the glycolytic cycle would be inhibited, the formation of glycogen would decrease, the oxidation of glucose would be diminished and, indirectly, there would be serious interference with the further metabolism of fat and protein. In other words, all of the metabolic derangements observed in diabetes mellitus could be explained upon the basis of an impairment of the hexokinase reaction in mammalian tissue. The hexokinase hypothesis of the diabetic defect therefore becomes a very attractive one and has received much discussion in the literature.

To obtain unequivocal evidence supporting the hexokinase hypothesis, systems must be used in which cell boundaries or cell-particulate interfaces between nutrilites and enzyme systems have been eliminated by appropriate means. Otherwise the effects observed could be equally well attributed to transfer or permeability changes brought about by hormonal action. The demonstration of a differential effect of hormones upon sugars other than glucose does not overcome this difficulty since it is always possible that hormonal effects upon transfer or permeability have a degree of specificity dependent upon the constitution of the sugar. Indeed such evidence is already in the literature.

Attempts to demonstrate altered hexokinase reactions in systems devoid of cellular barriers, for example extracts obtained from muscles of normal and diabetic rats, have been reported in the literature. The diminution of hexokinase activity reported was attributed to an excess of pituitary or adrenal factors. In this situation the addition of insulin *in vitro* was presumed to release the inhibition brought about by the adrenal and pituitary factors. An evaluation of the evidence in the literature, however (Stadie, 1954[41]), failed to substantiate these early claims. A summation of the evidence indicates that insulin, pituitary or adrenal factors, singly or together, have no influence upon the hexokinase reaction when this is determined in cell-free tissue preparations from normal or diabetic animals. It is worthwhile noting that the early equivocal evidence is frequently cited in the literature in support of the hexokinase hypothesis.

This negative evidence with extracts, however, does not necessarily rule out the possibility that in the intact animal or intact tissues *in vitro* it might still be possible to demonstrate a defect in the hexokinase reaction associated with the diabetic state. Two experimental approaches have been used for this type of study: The first is based upon the demonstrated fact that liver and muscle have separate hexokinases specific for glucose and fructose (glucohexokinase and fructohexokinase). If these hexokinases are not only specific with respect to their substrates but are also different in their response to insulin, for example, if glucohexokinase is insulin-sensitive and fructohexokinase is not, it would be expected that the metabolism of glucose would be affected in the diabetic state whereas fructose metabolism would be within normal limits. The second method of studying the hexokinase reaction in intact tissue is based upon the assumption that reactions in the glycolytic cycle beyond formation of glucose-6-phosphate are independent of insulin action and therefore are unaltered in the diabetic state. In consequence, therefore, the study of reactions involving members of the glycolytic cycle would shed light indirectly upon the involvement of the hexokinase reaction. Examples of both types of evidence will be cited.

Cori (1949)[9] discussed experiments in which glucose or fructose was injected into eviscerated rats and the effect of insulin upon the rate of utilization was studied. Typical data from their paper are shown in Figure 5. Sixty minutes after injection of the sugar the animal was sacrificed and the carcass analyzed for residual sugar. The calculated results support the glucohexokinase hypothesis since in the case of glucose injection of insulin markedly accelerated the rate of disappearance of injected glucose so that essentially none was recovered. In the case of fructose no acceleration of utilization was observed. Experiments employing glucose and fructose were reported by Renold, Hastings and Nesbett (1954).[33] In this study liver slices from normal and diabetic rats were equilibrated *in vitro* with the respective sugars. The use of isotopic glucose and fructose enabled the authors to calculate the utilization of these two sugars and the synthesis of glycogen from them. A summary of their data is reported in Table IX. The uptake of glucose was significantly diminished in the diabetic whereas that of fructose was essentially unaltered. However, it is to be noted that the synthesis of glycogen from both glucose

and fructose was markedly diminished. This would indicate that impairment of fructose metabolism also is a factor in diabetes. The authors, however, regard their data as indication that the chief if not the sole defect in diabetes is the impairment of the glucohexokinase reaction.

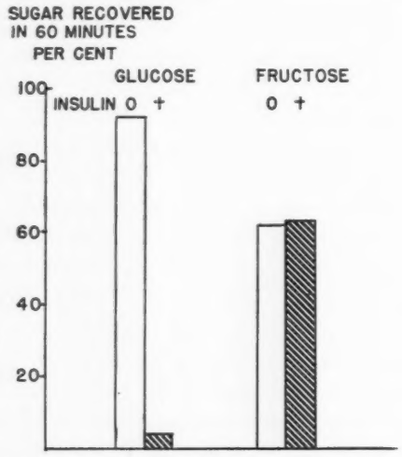


FIG. 5. Hexokinase theory of insulin action. Comparison of the effect of insulin upon the utilization of glucose and fructose by eviscerated rats; residual sugar (per cent of that injected) in the carcass was determined sixty minutes after injection. The increase in the utilization of glucose following insulin injection is assumed to be due to the acceleration of glucohexokinase; in contrast, the absence of effect with fructose is presumably because fructohexokinase is not affected.[9]

Experiments involving this second assumption are illustrated by data (Fig. 6) from a paper by Teng, Sinex, Deane and Hastings (1952).[50] They equilibrated liver slices from diabetic-adrenalectomized and normal rats with glucose or pyruvate. In the case of the diabetic-adrenalectomized rat maximum affects should be observed. They reported that in the diabetic-adrenalectomized rats synthesis of glycogen from glucose was markedly diminished whereas that from pyruvate was essentially unaltered. The authors concluded that "If the hexokinase hypothesis is correct, one would anticipate a decrease in glycogen synthesis from glucose but normal glycogen synthesis from pyruvate. Such indeed are our findings." A similar type of experiment was reported by Chernick and Chaikoff (1951).[7] They studied the metabolism of liver slices from normal and from alloxan-diabetic rats when equilibrated in isotopic glucose or fructose. Both CO_2 production and fatty acid synthesis were determined. The data (summarized in Table x) show that production of CO_2 and of fatty acids from labeled glucose was significantly diminished in the diabetic animal. On the other hand, fructose showed unimpaired production of CO_2 but diminished synthesis of fatty acids. On the basis of these data the authors concluded that the two hexokinases in the liver reacted differently to insulin. That for glucose was impaired by lack of insulin whereas that for fructose was uninfluenced. However, the lack of fructose incorporation into fatty acids in the alloxanized

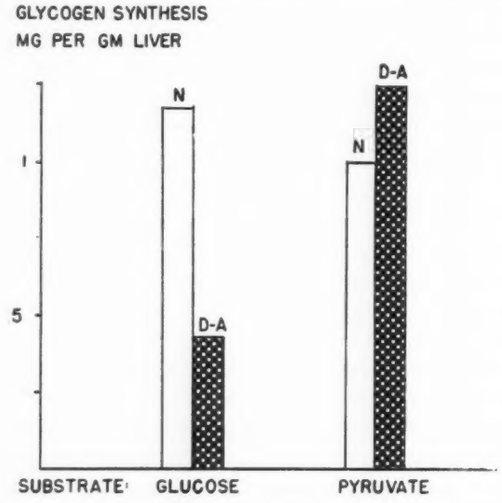


FIG. 6. Hexokinase hypothesis of insulin action; synthesis by liver slices from normal (N) or diabetic-adrenalectomized (D-A) of glycogen from isotopic glucose or pyruvate. Synthesis from glucose by D-A rat liver was depressed; conversion of pyruvate to glycogen was not found to have been impaired in D-A rat liver slices. The authors conclude that the results are in accord with the hypothesis that hexokinase activity in tissues is impaired.[50]

TABLE IX
CONTRAST OF GLUCOSE AND FRUCTOSE METABOLISM BY LIVER SLICES FROM NORMAL AND DIABETIC RATS[32]

	Micromoles per Gm. in 90 Min.	
	Normal	Diabetic
Total uptake		
Glucose	37	14
Fructose	96	99
Glycogen		
From glucose	15	0.3
From fructose	18	2.5

preparation brought the authors to an additional conclusion, namely, that diabetes was associated with a dual block, one of which involved conversion of the 2-carbon-like compound to fatty acids.

Other experiments of these two types have been offered as evidence that the hexokinase reaction in intact tissue is involved in the diabetic state. Can these conclusions be accepted? Only with reserve because evidence for the involvement of a "transfer mechanism" in the diabetic state is so strong that it cannot be excluded as governing the entrance of certain sugars into the sphere of action of enzyme systems. This makes it difficult to determine whether the deceleration or acceleration of metabolic reactions by endocrine disturbances is due to action on specific enzymes such as hexokinase or on some mechanism, still undetermined, which accelerates passage of substrates across cellular barriers.

TABLE X

COMPARISON OF PRODUCTION OF CO_2 AND FATTY ACIDS FROM ISOTOPIC GLUCOSE AND FRUCTOSE BY LIVER SLICES FROM NORMAL AND DIABETIC RATS[7]

	No. of Rats	Sugar Recovered from Slices, Per cent			
		Glucose		Fructose	
		CO_2	Fatty Acids	CO_2	Fatty Acids
Normal	6	4.0	0.59	6.8	0.82
Diabetic	6	1.1	0.02	6.2	0.10

3. Effect of Insulin Upon Oxidative Phosphorylation. The metabolic schema shown in Figure 1 indicates that the oxidative reactions of the Krebs cycle are concerned with the generation of energy-rich phosphate bonds (ATP, and so on). These bonds are involved in a large number of reactions such as the formation of glucose-6-phosphate by the hexokinase reaction, synthesis of fat and protein, and so on. The hypothesis cannot be excluded that a deficiency in the generation of these energy rich phosphate bonds might be a factor in the disturbed metabolism of diabetes mellitus. Many papers have been published presenting experimental evidence which is interpreted to support this hypothesis.

Early work on phosphate metabolism in the normal and in the diabetic, and the effect of injected insulin thereon, has been reviewed. (Stadie, 1954).[41] Both *in vivo* and *in vitro* analyses have been carried out on liver and muscle in which the various phosphate compounds such as glucose-1-phosphate, glucose-6-phosphate, ATP, ADP and inorganic phosphate have been separated and quantitated. The relations among these substances have been determined following the injection of glucose or glucose plus insulin. In addition, the rates of exchange o isotopic inorganic with organic phosphates following glucose or glucose plus insulin injections have been studied. Chief among the experimenters in this field are Kaplan and Greenberg (1944),[20–23] Sacks (1948, 1952, 1953)[37–39] and Haugaard, Marsh and Stadie (1951).[16] The results of these experiments are difficult to evaluate. In general, the evidence would lead one to conclude that some type of interference with the generation of high-energy phosphates is associated with the diabetic state or the action of insulin. On the other hand, none of the evidence enables one to determine unequivocally whether this influence is direct or merely secondary to effects of the general metabolic status of the tissue with respect to carbohydrate oxidation. For example, Sacks (1948)[37] calculated the rate of labile P turnover of ATP following the injection of P^{32}. These

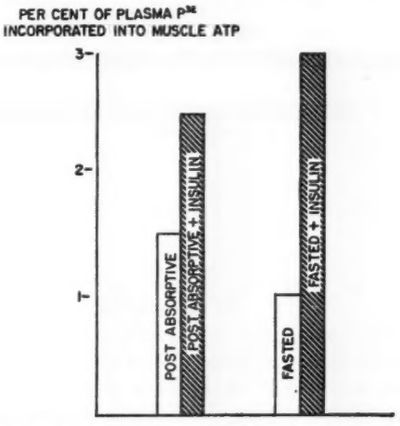


FIG. 7. Oxidative phosphorylation hypothesis of insulin action; the rate of incorporation of P in the blood into ATP of cat muscle following injection of P^{32} and insulin. Samples were taken for analysis three hours after insulin. Glucose was injected initially with the isotopic P in all instances. Insulin significantly increased the rate of turnover of P^{32} in ATP.[37]

results are indicated in Figure 7. Sacks (1948)[37] concluded that the administration of glucose and insulin brought about an increased rate of phosphate transfer across the cell membrane but he did not speculate as to the mechanism involved. Goranson, Hamilton and Haist

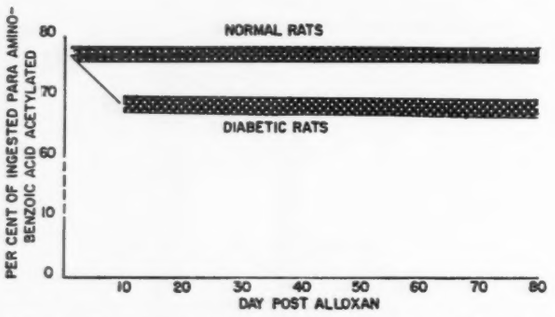


FIG. 8. Phosphorylation hypothesis; presumed impairment of oxidative phosphorylation leading to impairment of acetylation of injected para-aminobenzoic acid by diabetic rats. The hatched area indicates the approximate standard error of the data.[5]

(1948)[14] reported similar observations using tracer phosphates and suggested the possibility that insulin influenced oxidative phosphorylation bringing about accelerated formation of ATP. More direct evidence was reported by Charalampous and Hegsted (1949).[5] They studied the rate of acetylation of a foreign amine (para-aminobenzoic acid) when injected into the normal or the alloxan-diabetic rat.

This acetylation is known to be dependent upon the availability of high-energy phosphate. The results of these experiments (Fig. 8) showed a distinct impairment of the ability of the alloxan-diabetic rat to acetylate PAB. The authors pointed out that this decreased acetylation was restored to normal by the injection of insulin. Another reaction requiring high-energy phosphate, using rat liver homogenate, has also been studied by Foa, Weinstein, Smith and Greenberg (1952).[11] They studied the phosphorylation of thiamine using rat liver homogenates from the normal and from the alloxanized diabetic rat. A summary of their results is shown in Figure 9. In the alloxan-diabetic rat, compared to the normal, there was no diminution of total thiamine but the percentage of thiamine phosphorylated was significantly diminished.

These experiments, together with similar ones reported in the literature, constitute evidence of an indirect nature that high-energy phosphate formation is involved in the diabetic state. The first recorded evidence of a more direct character on this aspect of insulin action was reported by Stadie and Vester (1955).[46] The reactions of oxidative phosphorylation appear to be limited to the mitochondria. Therefore the comparison of the behavior of mitochondria from

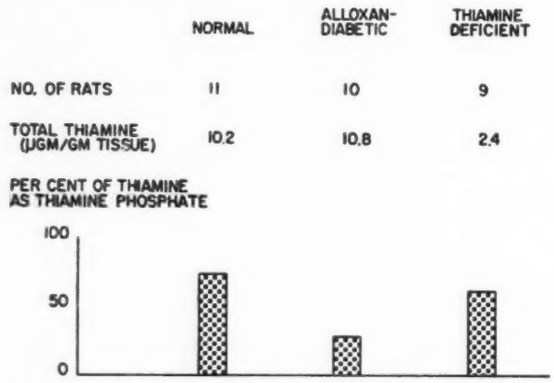


FIG. 9. Oxidative phosphorylation hypothesis of insulin action; diminution of phosphorylated thiamine in livers from alloxanized-diabetic rats.[11]

normal and diabetic animals with respect to ATP synthesis would constitute a fairly direct measurement of possible impairment of oxidative phosphorylation in diabetes. The mitochondria were obtained by the customary differential centrifugation of homogenates prepared from the liver of the cat. The washed

TABLE XI

OXIDATIVE PHOSPHORYLATION* BY LIVER MITOCHONDRIA PREPARED FROM LIVERS OF NORMAL AND DEPANCREATIZED CATS[46]

Cat No.	Pyruvate		β-Hydroxybutyrate	
	Normal	Diabetic	Normal	Diabetic
1	60	7	31	15
2	71	18	42	34
3	52	13	30	5
M	61	13	34	18

* Data gives rates of formation of adenosine triphosphate (μm per minute per mg. of mitochondrial protein) in presence of pyruvate or beta-hydroxybutyrate.

mitochondria were suspended in a buffer solution containing phosphate, pyruvate or beta-hydroxybutyrate. The high-energy phosphate formed as ATP was trapped as glucose-6-phosphate by combination with glucose catalyzed by added yeast hexokinase. The data (Table XI)

show that mitochondrial preparations derived from the liver of depancreatized cats were significantly deficient in their oxidative phosphorylation when pyruvate or beta-hydroxybutyrate were used as sources of energy. Simultaneous measurements of oxygen consumption made it possible to calculate the P:O ratio, which may be taken as a measurement of the efficiency of oxidative phosphorylation. This also was diminished in systems of mitochondria from diabetic cats. A later series of experiments of a similar character confirmed these preliminary observations. This direct indication of the impariment of oxidative phosphorylation observed in the liver of the depancreatized cat requires further exploration before its full significance can be evaluated.

4. Effects of Insulin on Oxidative Reactions in the Krebs Cycle. The possibility that the Krebs oxidative cycle may be a site of action of insulin is indicated in the schema of Figure 1. A number of papers have appeared in the literature supporting this possibility. Krebs and Eggleston (1938)[24] studied the effect of insulin upon oxygen uptake of mince of pigeon breast muscle. The type of data they reported is schematized in Figure 10. The oxygen uptake was measured in the presence and absence of insulin. They found that when catalytic amounts of members of the Krebs cycle (for example, citric acid or succinic acid) were present a typical effect was obtained. This consisted of prolongation of the ability of the muscle mince to take up oxygen. No significant acceleration of the oxygen uptake took place during the initial period but oxygen uptake with insulin continued for a much longer period than without, so that the total oxygen uptake might be doubled. The authors concluded from this type of experiment that "insulin is a catalyst concerned with one of the stages of citric acid cycle." These experiments with pigeon breast muscle have been confirmed. However, muscle from rabbits, cats and dogs appeared not to exhibit the phenomenon. Attempts to show a difference of behavior of normal and depancreatized cats were unsuccessful (Stadie, Zapp and Lukens, 1940[47]), nor was any effect of insulin observed in either of these preparations. These anomalous results have served to discredit the significance of experiments with muscle mince in the study of insulin action.

Other effects of insulin upon oxidative reactions have been reported. For example, oxidation of pyruvate by minces of pigeon breast muscle has been shown to be increased by insulin (Rice and Evans, 1943;[34] Stadie, Haugaard and Perlmutter, 1948).[43] The oxidation of pyruvate to CO_2 by rat diaphragm and heart ventricle slices from the alloxanized rate have

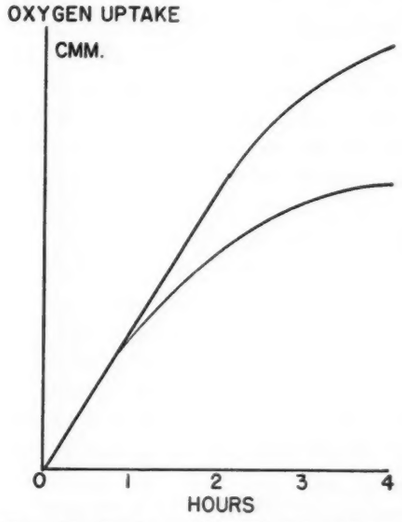


FIG. 10. Krebs cycle oxidations stimulated by insulin; the oxygen uptake of pigeon breast muscle mince + boiled muscle extract and catalytic amounts of citrate ± insulin. Insulin produces a more prolonged uptake of oxygen sometimes doubling the total uptake.[24]

been reported by Hastings et al. (1949).[31] They concluded from their experiments that there is "diminished ability of cardiac and diaphragm muscle to carry out the steps required to convert pyruvate to CO_2."

It is obvious from a consideration of the experiments discussed that a decision from the four possibilities of insulin action here outlined is impossible now. The situation is confused and alternative hypotheses rival each other in the weight of evidence massed for their support. In addition, it would be possible to collect other experimental evidence which would not fit into any of these hypotheses. It is possible that a synthesis of the conflicting evidence will be forthcoming in the near future which will resolve these contending difficulties.

RELATION OF INSULIN TO FAT AND PROTEIN METABOLISM

It is outside the scope of this review to discuss this area in detail. The summation of evidence indicates that there is no direct action of insulin

upon fat or protein metabolism. Disturbances of the metabolic pathways in question appear to be the indirect results of faulty carbohydrate metabolism, already discussed.

COMBINATION OF INSULIN WITH TISSUES

A brief discussion of this phenomenon is pertinent in any review of insulin action. It is well known that substrates combine with enzymes before they undergo chemical reaction. This phenomenon is formulated in the Michaelis-Menten concept which was well reviewed by Clark (1952).[8] Indeed, it would be difficult to imagine how the chemical reactivities of substrates could be influenced unless they came within the molecular distance of enzymes. Otherwise action at a distance would have to be invoked. A similar relationship must hold for the action of hormones upon enzymatic systems. The hormone must approach within molecular distance of the enzyme, otherwise it would be difficult to conceive how the hormone could affect enzymatic action. It is possible to conceive that this close approach of hormones to tissue would be of such nature that it could be characterized as a combination of a chemical character. At all events, a phenomenon first reported by Stadie, Haugaard, Marsh and Hills (1949)[42] was interpreted to indicate the possibility of such a combination of insulin with tissue. A rat diaphragm was momentarily dipped into a solution containing insulin and then thoroughly washed in saline. It was then equilibrated with glucose (no insulin being added) and after a suitable time was analyzed to determine the synthesis of glycogen. Compared to a hemidiaphragm from the same rat not treated with insulin, a marked increase in glycogen synthesis was invariably observed. This was interpreted to mean that during the momentary exposure to insulin the tissue had combined with it so firmly as to resist the disassociating action of washing. This combined insulin retained its customary metabolic effect on the diaphragm by increasing the uptake of glucose and the synthesis of glycogen. In later experiments Stadie et al. (1952 and 1953)[44,45] measured accurately the amount of insulin bound by using insulin tagged with iodine-131 or S-35. It was found that the metabolic activity of the bound insulin was proportional to the amount bound. In addition, the bound insulin was influenced by the hormonal state of the animal, being decreased in the alloxanized animal, in the rat injected with growth hormone or cortisone singly or together, and markedly increased in the case of the hypophysectomized rat. Further study of this phenomenon is necessary before complete evaluation is possible.

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Clinico-pathologic Conference

Exposure to Insecticides, Bone Marrow Failure, Gastrointestinal Bleeding, and Uncontrollable Infections

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, B. M. (No. 228986), a sixteen year old white schoolboy, was admitted to Barnes Hospital on November 9, 1953.

Five months before admission upon his return from a visit to California he was told by his family that his skin was pale. However, he felt well until two months before admission, at which time he complained of weakness, easy fatigability and malaise. He was seen by his local physician who gave him several medications, but weakness and fatigability continued. One month before admission the patient was referred to another hospital. Studies there were as follows: red blood cell count, 880,000 per cu. cm.; white blood cell count, 2,700 per cu. cm. The differential count revealed the following: juveniles, 2 per cent; band forms, 6 per cent; segmented forms, 6 per cent, and lymphocytes, 89 per cent. Hemoglobin was 12 per cent of normal. A bone marrow specimen was found to be markedly hypoplastic and a diagnosis of aplastic anemia was made. The patient was given twelve blood transfusions and was referred to the Barnes Hospital. There was no history of drug ingestion, bleeding manifestations, lymphadenopathy or of central nervous system symptoms. The patient had worked as a farm helper for two years and on several occasions he had been exposed to insecticides used for spraying fruit and animals. Among these were DDT, chlordane, and lindane.

Past history and family history were noncontributory.

Physical examination on admission revealed the patient's temperature to be 38°C.; pulse, 92; respirations, 16, and blood pressure, 140/90. The patient appeared chronically ill. The skin was pasty, but the color of the mucous membranes was good. Many small petechiae were scattered over the lower extremities. No icterus was present. Four spider hemangiomas were seen on the trunk. A few tiny anterior and posterior lymph nodes were palpable but no generalized lymph node enlargement was noted. The conjunctivae were clear. The fundi were normal except for one small hemorrhage. The tonsils were enlarged with a small amount of whitish exudate and several areas of hemorrhage on each. A few petechiae were present on the hard palate. There was ecchymosis and slight tenderness over the site of the previous sternal marrow aspiration. The lungs were clear. The heart was of normal size; a loud blowing systolic murmur was heard over the entire precordium. The liver was felt 6 cm. below the right costal margin and was non-tender. The spleen was not felt. Both testes seemed decreased in size, but the genitalia were normal. Rectal examination was not remarkable. Results of the neurologic examination were negative except for a left internal strabismus.

Laboratory data on admission were as follows: red blood cells, 4,420,000 per cu. mm.; hemoglobin, 14 gm. per cent; white blood cells, 4,400 per cu. mm. The differential count revealed the following: band forms, 2 per cent; segmented forms, 4 per cent; monocytes, 2 per cent, and lymphocytes, 92 per cent. Hematocrit was 46 per cent, and the indices were normal. Urinalysis showed the following: specific gravity, 1.030; reaction, 5.5; protein, negative, and

microscopic, normal. Examination of the stool revealed a negative guaiac test. Cardiolipin was negative. Blood chemistry was noted as follows: non-protein nitrogen, 22 mg. per cent; cephalin cholesterol flocculation, 3+; thymol turbidity, 2.8 units; total bilirubin, 1.1 mg. per cent; bone marrow, fatty marrow; the myeloid and erythroid series were markedly depressed. Many tissue basophiles were present. No megakaryoctes were seen. The findings were thought to be compatible with toxic depression. Throat culture revealed alpha hemolytic streptococci. Blood cultures gave negative results. Roentgenogram of the chest was within normal limits.

The patient was given penicillin, 800,000 units a day, and 20 mg. of ACTH in 1000 ml. of 5 per cent glucose in water by slow intravenous drip. During the first three days the temperature ranged between 38°C. and 38.5°C. and no change in his status resulted. On the fourth day the temperature spiked to 41.2°C. The area of the initial sternal aspiration was bulging, tense and fluctuant. Antibiotic therapy was increased. He was given 1,000,000 units of penicillin every six hours and 2 gm. of streptomycin daily. The fluctuant area over the sternum was incised, and about 30 ml. of organized blood clot were removed. No pus was found, and culture was sterile. Repeat blood cultures taken at the first temperature elevation also gave negative results. After surgery the temperature was elevated with spikes to 39°C. for three days, after which it gradually fell and became normal in about twelve days.

On the sixth day of hospitalization the patient passed several black stools which were guaiac negative; however, a few days later stool specimens were found to be guaiac positive. The urine contained no red blood cells. The hemoglobin fell slowly. On the ninth day of hospitalization examination of the blood revealed a red blood count of 2,490,000 per cu. mm., hemoglobin of 8.5 gm. and white blood count of 2,250 per cu. mm. Differential count was the same as that previously noted. At that time the patient was given 2 units of whole blood and thereafter required whole blood transfusions to maintain his hematocrit and hemoglobin levels. He continued to improve symptomatically. The area of the hematoma over the sternum slowly healed. On the fourteenth day of hospitalization the patient was given a daily dosage of 300 mg. of cortisone and 1 gm. of oxytetracycline. A repeat bone marrow aspiration on the twenty-ninth day of hospitalization showed no essential change from those previously examined.

The patient was allowed to go home over the Christmas holidays. He returned in two days; there had been no essential change during the interval. Two days after his return, however, he began to complain of severe pleuritic right anterior chest pain. He did not cough, but the temperature had risen to 39.5°C. Examination of the chest revealed no signs of consolidation, but splinting of the right chest was present. A roentgenogram showed a linear infiltration in the right lower lobe, thought to be indicative of pneumonia, associated with a minimal right pleural effusion. The oxytetracycline on which he had been carried for prophylactic reasons was continued but penicillin and streptomycin were added. The temperature remained elevated and the patient continued to have pain in the chest. Repeat blood counts revealed the following: red blood cells, 3,120,000; hemoglobin, 9.3 gm. per cent; white blood cells, 1,300 per cu. mm. The differential count was as follows: segmented forms, 20 per cent; lymphocytes, 80 per cent, and platelet count, 12,480 per cu. mm. Culture of the sputum isolated Friedländer's bacillus and Staphylococcus citreus. In spite of antibiotic therapy the fever continued, as did all symptoms. The patient began to complain of tenderness to light palpation over the anterior right chest. A repeat chest x-ray revealed partial resolution of the right middle lobe atelectasis which was thought to be present in the previous film. It also showed a partial clearing of the pneumonitis previously noted. A patchy destructive process was described at the anterior end of the fourth right rib, although this finding was subsequently questioned by several observers. Cortisone therapy was reinstituted because of the low platelet count, and erythromycin and chloramphenicol were added.

The patient seemed to improve for a short time. His temperature fell for the first time in five days to 37.2°C. but again rose, ranging between 38°C. and 39.5°C. He became pale and weak, his appetite diminished, and he began to bleed from the gums and from a large necrotic ulcer which appeared in the nose. Packs were of only partial benefit in controlling bleeding. The ulcers became more necrotic and continued throughout the remainder of his life. Blood counts continued to fall and the patient required constant blood transfusions. Subsequent roent-

genograms of the chest showed continuing resolution of the pneumonitis and atelectasis of the right middle lobe. More petechiae appeared in the skin. The stools became guaiac positive, and red blood cells appeared in the urine. Proptosis of the right eye was noted and slowly increased. This was not associated with pain, change in vision, or other neurologic signs. Results of lumbar puncture were within normal limits. Friedländer's bacilli were cultured from the sputum on two occasions. Culture thereafter contained non-hemolytic Staph. citreus and coliform organisms. Blood cultures gave negative results. Four days before death the patient began to complain of severe sore throat. The left tonsil was found to be large, red and boggy, and the next day a white exudate was present. Culture from this exudate showed a heavy growth of coliform organisms. Chloramphenicol therapy, which had previously been discontinued, was re-instituted. On the day before death the patient became apprehensive and dyspneic. The skin rapidly became markedly icteric. The temperature rose to 40°C. and the patient expired on February 9, 1954.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: The patient for discussion is a sixteen year old schoolboy with bone marrow failure who had been exposed to insecticides, both DDT and lindane, while working on a farm during the summer. The duration of the marrow failure at the time he came to the hospital in early November was at least two months and possibly five months. During the month prior to admission he had received twelve transfusions in another hospital. Abnormalities noted on admission included fever, petechiae, inflammation of the tonsils, systolic apical murmur, enlargement of the liver and large ecchymoses over the sites of the previous sternal bone marrow aspiration.

Laboratory data on admission were remarkable chiefly for the hematologic findings. The bone marrow was fatty with depression of all three of the important elements, the myeloid series, the erythroid series, and the megakaryocytes. Because of recent transfusions the peripheral blood on admission did not reveal any significant anemia, but this absence was short-lived. The white blood cell count varied from a high of 4,600 with 20 per cent granulocytes, to a low of 360 with no granulocytes present. It was implied in the protocol but not so stated that there was persistent thrombocytopenia, the highest platelet count being recorded as 44,000 on the third day of hospitalization. On the fourth day his temperature, which had been between 38°C. and 38.5°C., rose to 41°C. Meanwhile, ACTH and prophylactic oxytetracycline were given. The cause of this initial fever was uncertain. Possibly it was due either to the pharyngitis or to the fluctuant site of the sternal marrow aspirations done elsewhere, although cultures of this material gave negative results. In any event, with administration of penicillin and streptomycin added to that of oxytetracycline the temperature gradually returned to normal over a twelve-day period. During the next five weeks he remained afebrile, receiving prophylactic oxytetracycline and penicillin plus cortisone. No evidence of bone marrow activity was found. He was allowed to go home over the Christmas holidays while taking the drugs and returned after two days. Two days later the final stage of his illness began with fever and right pleural pain. Friedländer's bacilli were cultured twice from the sputum. Penicillin and streptomycin were again added to the oxytetracycline, and almost all available antibacterial agents were used subsequently with some success, at least from the standpoint of the pulmonary lesion. Meanwhile, only a few days after the onset of pulmonary difficulty, epistaxis began which required nasal packing. Infection developed at this site and progressed until the time of his death one month later. Bleeding from this and from other sites constituted a real problem. Three days after the onset of the cellulitis of the nose proptosis of the right eye was detected, and the possibility of sinus thrombosis was raised. Results of neurologic and spinal fluid examinations were normal. The patient remained febrile with a spiking temperature without evidence of a localized infection other than the aforementioned pulmonary lesion and cellulitis of the nose. Arthralgia and myalgia were thought to be the result of transfusion reactions. Four days before death pharyngitis recurred; coliform organisms were recovered from the pharynx, and on the day before death jaundice appeared. May we see the x-rays?

DR. GLADDEN V. ELLIOTT: The pertinent radiographic examinations were limited to the chest, of which there were several examinations made prior to his death. The initial examination on his first admission to the hospital on November 10 served as an excellent base line; it was

within normal limits. The first abnormalities were noted on his return to the hospital after the Christmas holidays. The examination on December 29 showed an obvious dense localized discrete infiltration of the right lung base which in the lateral view was somewhat difficult to see, but probably occupied primarily the middle lobe. The diaphragm on the right side was markedly elevated. A little pleural effusion was noted in both the anterior and posterior gutter. Over the next month there was a slow but incomplete resolution of this pneumonic process with persistence of some shrinkage or atelectasis of the middle lobe segment. During the month a destructive process in the anterior end of the fourth rib was questioned several times. Our final film was a laminagram exposed on January 15 in an attempt to further delineate this fourth rib anteriorly. At the time of this laminagram no apparent involvement of that fourth rib was noted. The cortices appeared intact throughout.

DR. SCOTT: Dr. Loeb, before I ask Dr. Shank to review the toxicology of the insecticides to which the patient had been exposed, would you further define the nature of the hematologic problem and mention something of the correct terminology which should be employed in such instances.

DR. VIRGIL LOEB, JR.: If one is confronted by a patient presenting the clinical story, as did this boy, of weakness, easy fatigability, fever without obvious infection, bleeding tendency, and laboratory evidence of anemia, thrombocytopenia, and granulocytopenia, immediately one would think of two diagnoses, either acute leukemia or bone marrow failure. The diagnosis of acute leukemia was ruled out early in his illness by the finding of hypoplastic bone marrow and by the absence of peripheral lymph node enlargement. The term "bone marrow failure" is applied here simply as a generic term meaning that the bone marrow fails to produce its normal complement of cells; in this case all three cellular types were affected, resulting in the absence of red cell production, granulocyte production and platelet production. In this particular case, since the bone marrow was actually morphologically aplastic, the term "aplastic anemia" can be applied. It is in those cases where the same peripheral blood picture is noted and the bone marrow appears normally cellular that the term aplastic anemia is incorrect, and for that reason the term "bone marrow failure" is preferable. The cases of aplastic anemia may be divided into main etiologic categories, on the one hand those due to an endogenous or idiopathic cause for which no known etiology can be demonstrated or, on the other hand, those due to an exogenous cause, in most cases a chemical, a drug, irradiation or some physical agent. Certainly the picture following irradiation or exposure to radioactive isotopes is comparable to the situation in this case, but the most likely diagnosis here would be based on past history of exposure to a known bone marrow toxin, either DDT or lindane.

DR. SCOTT: With respect to the term "aplastic anemia," isn't it true that the anemia is the least important of the difficulties, red cells being reasonably easily replaced, whereas the absence of white cells and platelets is more difficult to manage.

DR. LOEB: From the standpoint of therapy, perhaps anemia is the least difficult to manage; certainly when the platelets and granulocytes are decreased one runs into one complication after another, such as those manifested in this case.

DR. SCOTT: Dr. Shank, would you review briefly the toxicology of these two insecticides?

DR. ROBERT E. SHANK: This patient was exposed to and had used DDT and lindane during two summers, first in the summer of 1952, then more recently in the summer of 1953. It became important to examine the possible relationship of his exposure to the occurrence of pancytopenia. In reviewing the literature one finds that both DDT and lindane (benzene hexachloride) have been judged to be implicated in the production of thrombocytopenia, agranulocytosis and in the decrease of red blood cell formation.[1,2] Lindane seems particularly culpable in this regard. Much more DDT has been used in the United States and throughout the world than has lindane, but the number of cases reported of pancytopenia resulting from the use of lindane is much greater. We felt that of the insecticides used here, lindane was more likely to be the responsible agent. In examining the history more closely we found that during the summer of 1953 there was one period when

[1] FRIBERG, L. and MARTENSSON, J. Case of panmyelophthisis after exposure to chlorophenothane and benzene hexachloride. *Arch. Indust. Hyg. & Occup. M.*, 8: 166, 1953.

[2] DANOPOULOS, E., MELISSINOS, K. and KATSAS, G. Serious poisoning by hexachlorocyclohexane: clinical and laboratory observations on five cases. *Arch. Indust. Hyg. & Occup. M.*, 8: 582, 1953.

the boy sprayed a large group of cattle with a mixture that contained both DDT and lindane. He used it for about half a day during the morning, then had to leave his work for twenty-four hours. During this period he stated that he was weak, became nauseated and then vomited. The symptoms described are those which might occur with acute toxicity due to lindane. It was not until two months later that he was noted by friends to be pale, and it was even later than that when bone marrow failure was actually noted. I would like to conclude by stating that these insecticides are probably highly toxic for the bone marrow.

DR. SCOTT: The additional information that you have given about his spraying of the cattle was not in the hospital record, and it provides more support for insecticide toxicity than we had. I understand that some *in vitro* studies using lindane were made. Do we have any information about those studies?

DR. LOEB: To the best of my knowledge they were all inconclusive and showed no evidence of an immunologic mechanism responsible for the thrombocytopenia.

DR. SCOTT: Dr. Moore, before we get into the subject of treatment, what can be said about the prognosis in a situation such as this when patients have bone marrow failure allegedly due to some toxic agent, either drug or insecticide? Also, is the appearance of the bone marrow of any value in estimating the prognosis?

DR. CARL V. MOORE: The first thing one can say is that when the white cell count and the platelet count are markedly depressed the prognosis is worse than when those values are reasonably near the normal. Secondly, when the marrow is hypocellular over a period of a week or two, eliminating just a transient hypocellularity, the prognosis is certainly worse. There are recoveries. One does see persons who develop hypocellular marrows from benzene and other toxic agents with severe leukopenia and severe thrombocytopenia who gradually over a period of many months do recover. Those patients, however, certainly are the exception rather than the rule, and probably nothing we do brings about recovery. They simply recover by themselves, as far as we know.

DR. SCOTT: The objectives of treatment then are to prolong life until such time as bone marrow may begin again to function spontaneously?

DR. SCOTT: Such an attempt was made in this boy.

DR. SCOTT: In attempting to achieve these objectives, two main therapeutic approaches were utilized. The first of these was the use of cortisone. Dr. Loeb, I believe you were on hand when the decision to use cortisone was made. Would you tell us what was hoped for by utilization of this agent?

DR. LOEB: The only reason for giving cortisone to this boy was, as Dr. Moore said, to attempt to prolong his life so that he could ultimately recover on his own. There is a well recognized effect of cortisone upon the preservation of vascular integrity in thrombocytopenic states which seems, for some reason not clear to me, to prevent spontaneous bleeding even though the platelet level is low. There doesn't seem to be much evidence that cortisone under conditions of bone marrow depression can stimulate platelet formation, but there is good clinical evidence and some experimental evidence that cortisone will at least prevent some spontaneous bleeding through the capillary wall in thrombocytopenic states. It was for that reason alone that it was felt cortisone therapy was justified, an attempt thereby being made to stop the spontaneous hemorrhages which are usually the cause of death in these cases.

DR. SCOTT: Then there were two aspects for which cortisone was used: first, in the hope that it might in some way stimulate the bone marrow; second, and more important, for its non-specific effect in helping to maintain capillary integrity. Of course, in this instance, as the patient has no granulocytes, the use of cortisone is a two-edged sword. We are all familiar with the fact that patients who are receiving cortisone, for reasons not entirely clear, are prone to infections of one kind or another.

Dr. Wood, we know that you are interested in the effects of cortisone experimentally upon leukocytes. I wonder if you would summarize briefly for us what these effects may be. And, since this patient had so few granulocytes, would you express an opinion as to whether cortisone would have been any more detrimental under these circumstances. In what other way does cortisone effect the defensive processes of the body?

DR. W. BARRY WOOD, JR.: We have been interested in studying the effect of cortisone on infections. It is clinically well-known that patients on cortisone therapy tend to acquire infections. Some of our earliest experiments were done in Dr. Glaser's laboratory with streptococ-

cal pneumonia and we were able to show that cortisone would depress the inflammatory reaction in the lung. What you see in that situation is the failure of the leukocytes to penetrate into an infected area in the large numbers that characterize their behavior in the normal animal. In other words, there is an anti-inflammatory effect of cortisone. But once the leukocytes get to the infected area they do a good job of destroying bacteria. Our experiment suggests that the cortisone acts primarily by preventing the leukocytes from getting into the infected site by the usual mechanism of diapedesis. Dr. Fred Allison has been studying the problem in the rabbit ear chamber to determine in what way cortisone stops the leukocytes from getting into the infected area; he has had to work out a tricky method of producing an inflammation in the rabbit ear chamber in which he can show that cortisone seems to prevent the entire sequence of events ordinarily following inflammatory stimulus. In other words, if cortisone is given first there is no change in the blood vessels, whereas usually the blood vessels dilate at the beginning of an inflammatory response, then the leukocytes stick to the wall of the vessel, crawl through and into the infected area. Cortisone stops all this. Our present idea is that cortisone must work at a very early phase of the inflammatory mechanism and stop it from being set off. What that involves we don't know, because we don't know what sets off an inflammatory reaction.

In answer to your second question about using cortisone in the presence of agranulocytosis, there is no doubt that the hormone is more dangerous to use under those circumstances since the absence of leukocytes is the loss of one of the main body defenses. If one inhibits further the migration of those few leukocytes into the infected area, the situation is certain to become worse. In treating this boy, I am sure everyone realized what was going to happen, and they tried to protect him with antibiotic therapy. At the present time one can't say too much more about the effect of cortisone on infections except to point out that dosage is extremely important. If an experiment is properly set up in the laboratory one can demonstrate that cortisone protects an animal against infection. To do this very small doses of cortisone must be used. If the dosage of cortisone is increased to the range used in this case one gets the anti-inflammatory effect and, of course, less resistance to infection. So, as with many other experiments, either result can be attained, depending upon the dosage. What we have to worry about here, of course, is the big dosage with its anti-inflammatory effect and the greater susceptibility of the patient to infection.

DR. SCOTT: Is the immunologic response in the animal altered?

DR. WOOD: The immunologic response is very difficult to say anything about at the moment because of the conflicting evidence. There are those who have demonstrated that antibody production can be depressed by the use of cortisone and ACTH. Other reliable investigators have shown that that is not true of certain antigens, that antibody production is just as great with cortisone. The latest information is that cortisone will depress antibody production, depending upon the size of the antigen; if the antigen is large enough, cortisone will depress antibody production, whereas with relatively small antigens, such as polysaccharides obtained from bacteria, cortisone has no effect on antibody response.

DR. SCOTT: One of the objectives of treatment with cortisone, then, was the prevention of bleeding; this in the final analysis was not very successful. The second objective of treatment was the prevention of infection, and for this purpose penicillin and oxytetracycline were utilized prophylactically. Dr. Glaser, you are interested in penicillin prophylaxis under somewhat different conditions in the normal person rather than in the person without granulocytes. What kinds of infection can one hope to prevent with penicillin?

DR. ROBERT J. GLASER: There are some that one can prevent with penicillin, particularly hemolytic streptococcal infection, probably pneumococcal infections and, less predictably, staphylococcus infections, although these have become very resistant to penicillin in a large percentage of cases. Little can be done with any of the gram-negative rods or with any other microorganisms. Penicillin is a fairly limited tool and ought to be used under restricted circumstances.

DR. SCOTT: Do you think it should have been used under these circumstances?

DR. GLASER: In this case one had to give the patient the benefit of the doubt. Here, of course, much larger dosage was used and rightly so.

DR. SCOTT. Dr. Harford, what about the experience with oxytetracycline? Is the experi-

ence, using this agent prophylactically, extensive enough now to predict what can and what cannot be prevented with this agent?

DR. CARL HARFORD: There is not enough information to be able to make an accurate statement on that point.

DR. SCOTT: In early January, then, the patient developed pneumonia and Friedländer's bacilli were cultured from his sputum on two occasions. On both occasions the reports state that a heavy growth of Friedländer's bacilli was obtained and that the organism killed a mouse. Is that good evidence that the pneumonitis present was caused by this agent?

DR. HARFORD: It is fairly strong evidence, but it is not conclusive, because heavy growth of similar organisms may be obtained from the respiratory tract of persons who have no clinical manifestations of respiratory infection.

DR. SCOTT: Will any Friedländer's bacillus kill a mouse?

DR. HARFORD: That takes us back to the matter of classification. We have chosen to use the term to mean an encapsulated gram-negative coliform bacillus which can kill a mouse; simply because of the importance of capsules in virulence, we think that point has clinical significance, although people who spend time classifying bacteria might not agree, on the basis of such evidence, that this was Friedländer's bacillus.

Dr. Scott: So part of our evidence here that this was Friedländer's bacillus was that it killed a mouse. What about the sensitivity of this organism to oxytetracycline?

DR. HARFORD: The organism grew in 50 μg. per ml. of polymyxin. It grew in 10 ml. of oxytetracycline with partial growth at 20 and 30 μg. So it was moderately sensitive under the conditions of this test.

DR. SCOTT: The other infection which developed was the cellulitis of the nose; from this nothing of significance was cultured. A light growth of proteus and a moderate growth of staphylococcus albus were present which were non-hemolytic and coagulase-negative.

This patient was in the hospital for ninety days. He received eighty-five days of steroid treatment and a total of 198 days of antibiotic treatment, including sixty-three days of oxytetracycline, forty-nine days of parenteral penicillin, three days of tetracycline and twenty-three days of chloramphenicol. For fifteen days he received one antibiotic, for forty-six days two antibiotics, for twenty-five days three antibiotics, and for three days four antibiotics. For almost a third of his hospital stay he was receiving more than two antibiotics each day. Now, Dr. Reinhard, since chloramphenicol is an agent which has been described as producing this type of hematologic difficulty, do you think it was justifiable treatment in this circumstance?

DR. EDWARD REINHARD: This is a problem that comes up many times, and one has to keep in mind that medicine is very often a question of analyzing statistical probabilities. This man had a very serious illness which certainly constituted an immediate and desperate threat to his life. He had a severe infection, and the chances of his succumbing to this infection were great. The probability that he would be sensitive to chloramphenicol was no greater than the chance of anyone else being sensitive to it. Probably in not more than one of several hundred thousand people receiving chloramphenicol will aplastic anemia develop due to this drug, so that if he had had an infection more sensitive to chloramphenicol than to any other available antibiotic, it should by all means have been used.

DR. SCOTT: Is there any evidence that the duration of chloramphenicol treatment has anything to do with the development of this type of reaction? Can a reaction be evoked as frequently from one day of treatment with chloramphenicol as with a month's administration?

DR. REINHARD: The same principles that apply to other drugs probably apply here. If a patient had had previous chloramphenicol therapy he might have a severe blood reaction of this sort from a single tablet; if, on the other hand, he had never received the drug it would probably require a week or ten days before such a reaction would take place, if it took place at all.

DR. SCOTT: Now we come to the terminal part of the illness. You will recall that he remained febrile despite all these antibacterial agents. His bone marrow showed no response. Infections in the nose persisted. The pulmonary lesion apparently did not progress. One aspect of his illness about which we have little information is the fact that jaundice developed on the day before he died. Dr. Shank, what about the jaundice? Do you think this was homologous serum hepatitis or widespread bacterial infection of the liver. Is the information we have too meager to allow us to guess?

DR. SHANK: When the patient was admitted to the hospital his liver was described as large but non-tender. Yet at that time liver function tests included a cephalin flocculation of 3+, a thymol turbidity within normal range and a total serum bilirubin that was just 1.1 mg. per cent. Since this involvement developed so late, relative to the findings described earlier, it is a little difficult to assess. I suppose it should be stated that he might have had homologous serum jaundice. On the other hand, he might have had some form of hepatic disease on admission; both of the insecticides to which he had been exposed do, on chronic exposure, produce hepatic damage. Little laboratory evidence of that type of disease was found. I am afraid I cannot go further in giving you a specific answer to your question.

DR. SCOTT: Dr. Loeb, do you think there was sufficient bleeding into the skin and internal organs to account for the development of jaundice in this patient.

DR. LOEB: I have no basis on which to say yes or no. I think it is a good possibility, especially if the liver was jeopardized and could not clear the bilirubin due to increased hemolysis.

DR. REINHARD: I would say that the jaundice here was probably due, as has been previously stated, to a combination of at least two causes: first, a certain amount of liver damage probably present at the time of admission to the hospital which could have been due to exposure to hepatoxic chemicals or possibly to the overwhelming infection; second, to the rather extensive hemorrhage occurring in internal organs.

DR. SCOTT: The clinical diagnoses here were (1) aplastic anemia due to exposure to insecticides, (2) pneumonia, right middle lobe and (3) hepatitis due to toxins.

DR. SHANK: It would be well to point out to physicians that there are electrical vaporizers on the market which heat crystals of lindane and chlordane to provide a continuous or intermittent mist of these chemicals. These are commercially advertised as effective home or farm insecticides and are designed to be used on porches or in areas where insects are a nuisance. It should be obvious that such devices constitute a serious health menace,[3] and in my opinion, should be taken off the market.

[3] Health problems of vaporizing and fumigating devices for insecticides. *J. A. M. A.*, 152: 1232, 1953.

PATHOLOGIC DISCUSSION

DR. ROBERT W. OGILVIE: At autopsy the skin was icteric. A necrotizing inflammation involved the anterior nares. Numerous petechiae and ecchymoses were scattered through the skin, mucous and serous membranes, lungs, heart, kidneys, testes and retroperitoneal tissues. The bone marrow of the ribs, vertebrae and sternum appeared grossly hypoplastic, while that of the femur and tibia was yellow and fatty. The liver was enlarged, weighing 2,580 gm., and revealed no apparent necrosis or fibrosis. The spleen was of normal size and gross appearance. The cervical, tracheobronchial, periportal and mesenteric lymph nodes were moderately enlarged, firm, discrete and red-brown. Multiple petechiae and firm focal hemorrhages measuring up to 3.5 cm. in diameter were scattered throughout the lungs; however, none of these foci had the usual gross appearance of bronchopneumonia. The middle lobe of the right lung was fibrous and contracted. It was adherent to the anterolateral thoracic wall beneath the right fourth rib. The rib was increased in diameter at this point and the periosteal tissues were thickened, firm and grey with soft, necrotic, and yellow-brown areas. The kidneys were enlarged and weighed 325 and 340 gm. Their parenchyma was pale and contained multiple petechiae. In the pelves bilaterally extensive hemorrhages were noted. A small abscess was present in the cortex of the left kidney.

DR. DAVID E. SMITH: Dr. Ogilvie has described for you the extensive hemorrhagic manifestations present in this case. Figure 1 is a picture of the stomach (gross) to show how impressive some of the mucosal hemorrhages were. A large ulcerated area of gross hemorrhage lay in the lower part of the esophagus, and the mucosa of the corpus and fundus of the stomach down to a sharp line in the pylorus was congested and filled with extravasted blood. The same type of hemorrhage was present in the renal pelves and was represented in parenchymatous organs by ecchymoses in many sites.

A microscopic section of the bone marrow is illustrated in Figure 2. This particular section is from a vertebra; however, it is representative of all sections from the usually hematopoietic marrow. Small foci of granular debris represent active necrosis, and an almost completely exhausted appearance, as far as any single

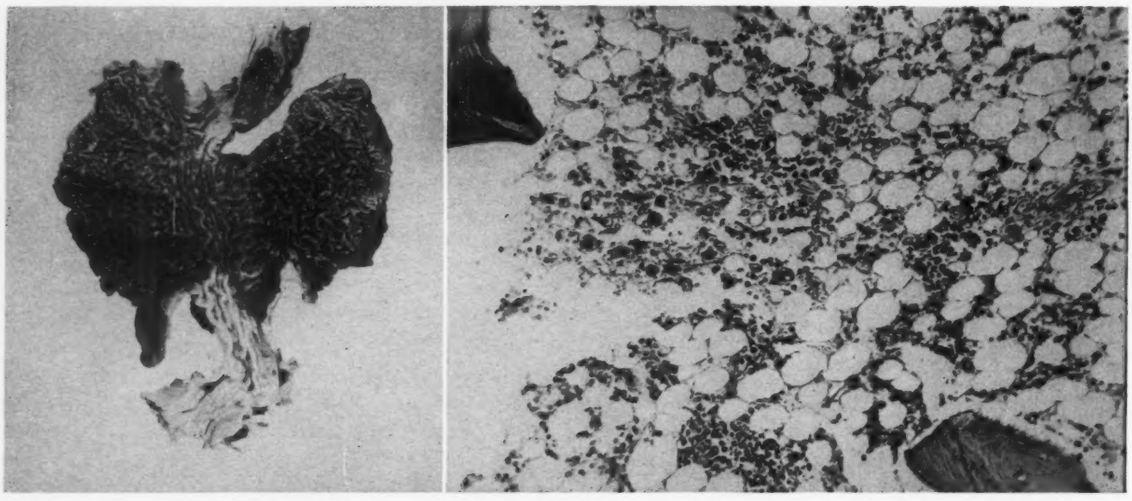

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FIG. 1. Extensive hemorrhage in the mucosa of the corpus and fundus of the stomach with sparing of the pyloric region. The esophagus in the upper part of the illustration has a large hemorrhagic ulceration in the lower portion.

FIG. 2. Foci of necrosis and generalized hypoplasia of the bone marrow in a vertebra. The remaining cells are plasma cells, reticulum cells, and a few representatives of the granulocytic series, but no megakaryocytes are present.

hematopoietic cell is concerned, characterizes the remainder of the section. The scattered cells remaining are a few plasma cells and representatives of various series, particularly the granulocytes. It is notable that practically no megakaryocytes are present in this or any other section.

The liver is histologically fairly normal. (Fig. 3.) There is a little fatty metamorphosis around the central veins, and a few large hepatic cells suggest a regenerative activity that might be interpreted as evidence of a residual of toxic damage, but nothing justifies a morphologic diagnosis of active viral or toxic hepatitis. The icterus, therefore, seems to have developed on the basis of extensive extravasation of blood in various tissues and widespread infection in many organs, although neither bacteria nor inflammation are apparent in the liver itself.

In a typical lymph node illustrated in Figure 4 there are large colonies of bacteria that are largely cocci. These gram-positive cocci were not identified by culture; however, the blood yielded in addition a profuse growth of colon bacilli and a diphtheroid. The lymph nodes were further remarkable for the presence of edema in the sinusoids and a remarkable hyperplasia of reticulum cells and other large mononuclear cells. Abscesses in the other organs such as the kidneys were also characterized by tremendous growth of bacteria and the lack of any evidence of polymorphonuclear leukocytes in their walls.

The lesion of the right fourth rib was a large subperiosteal abscess and a section from its wall is shown in Figure 5. Here again there can be seen large masses of bacteria and the same type of granulation tissue with a mononuclear exudate instead of polymorphonuclear leukocytes. Above the capsule of the abscess there is a wide collar of recently formed bone that is almost as thick as the normal rib and which apparently has arisen in response to the inflammation in the periosteum.

The final section (Fig. 6) is from the lung. It is representative of the hemorrhagic nodules which were present throughout all lobes. Hemorrhage into the alveoli, large masses of fibrin in the alveolar spaces, and practically no cellular reaction were the predominate features of these nodules. In other sections large numbers of bacteria were associated with this type of lesion, which represented the effects of a bacterial infection of the lung that had led to the breaking down of capillaries and escape of fibrin and red cells into the alveoli without having the usual polymorphonuclear leukocytes present to be called upon to participate in the morphologic response. It can be very appropriately called an agranulocytic pneumonia. The area in the middle lobe of the right lung that corresponds to the shadow in the roentgenogram was an organized pneumonia. It could have resulted from a similar although less severe pneumonia of this atypical type, although in its final form it

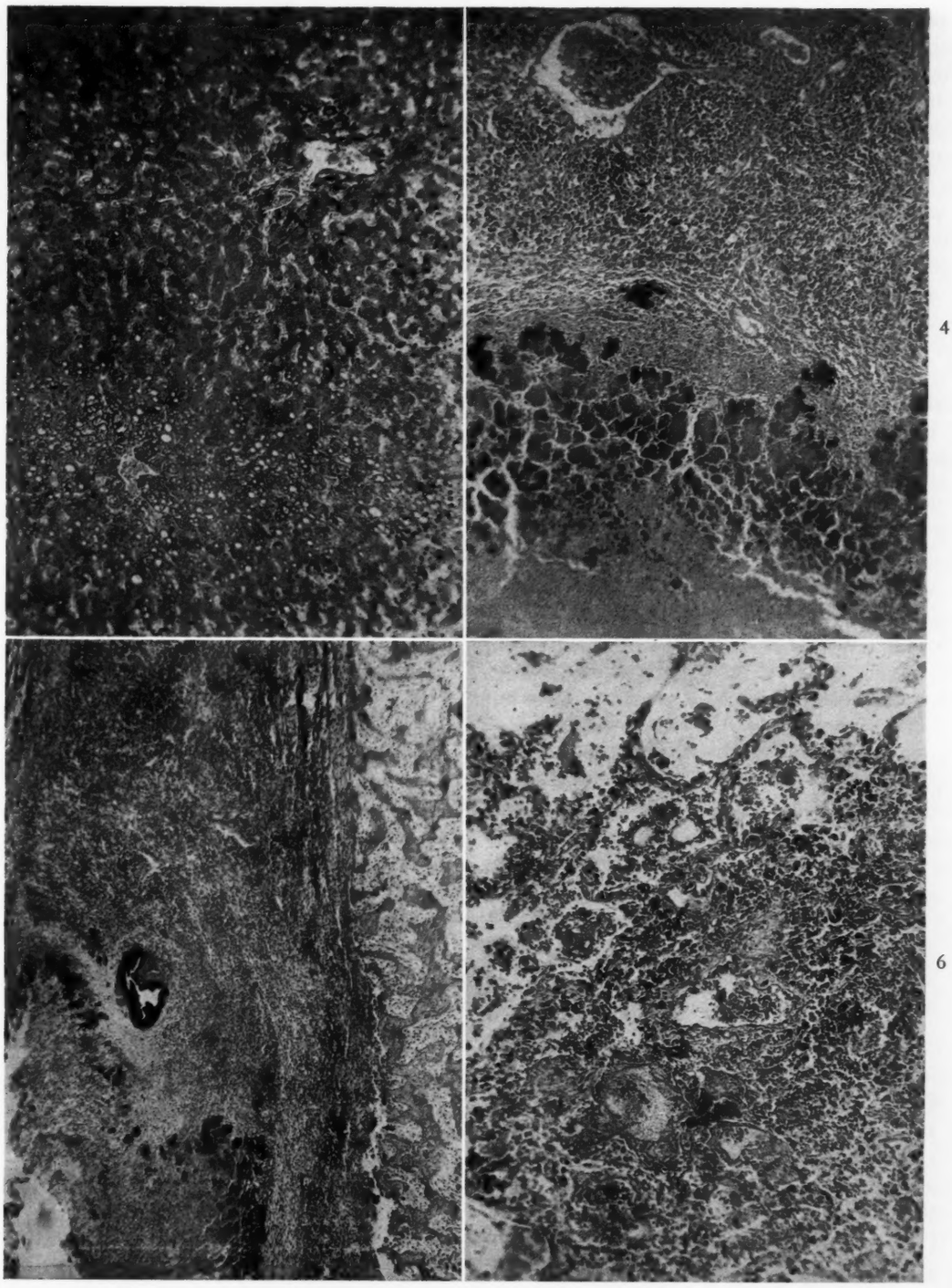

FIG. 3. Centrolobular fatty metamorphosis and atrophy of the liver without necrosis or other evidence of a toxic or infectious hepatitis.

FIG. 4. A cervical lymph node with a large abscess in which there is extensive bacterial colonization and little cellular reaction in the wall. The parenchyma on the left is composed almost entirely of hyperplastic reticulum cells.

FIG. 5. The subperiosteal abscess of the right fourth rib with the same colonization of bacteria and lack of polymorphonuclear leukocytes as those seen in the lymph nodes. Above the abscess is a portion of bone that has been newly formed in response to the irritation of the periosteum.

FIG. 6. An agranulocytic pneumonia with fibrin, hemorrhage, mononuclear cells and bacteria in the alveoli, but no polymorphonuclear leukocytes are present.

was not appreciably different from any other organized pneumonia.

The tissue responses in this patient were primarily an almost total aplasia of the bone marrow and no evidence of regenerative activity or extramedullary hematopoiesis in any organ. These changes have no specific characteristics that would enable one to identify them as the effects of a particular causal agent, but they are perfectly compatible with the changes of toxic aplasia that can occur after such agents as lindane, and the history supplied by Dr. Shank makes it seem quite likely that that was their etiology. In addition there were the effects of an extensive spread of bacteria throughout the body during the last weeks or days of life.This resulted in the formation of abscess walls that were atypical because of the lack of their usual component of polymorphonuclear leukocytes, yet which represented considerable effort on the part of the tissues to combat the infection. Finally, there were extensive hemorrhages that apparently were due to the lack of platelets and to the septicemia and which led to the icterus without specifically involving the liver.

Final Anatomic Diagnoses: Aplastic anemia; septicemia with abscesses in the kidney and periosteum of a rib; reticulum cell hyperplasia of lymph nodes; agranulocytic pneumonia; petechiae, ecchymoses and hemorrhages in all organs.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

Research Society Abstracts

Western Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EIGHTH ANNUAL MEETING, CARMEL, CALIFORNIA, JANUARY 28 AND 29, 1955

PRODUCTION OF RENAL CORTICAL NECROSIS WITH SEROTONIN (5-HYDROXYTRYPTAMINE). *Ernest W. Page,* and Mary Beth Glendening.* Dept. Obstetrics and Gynecology, Univ. California School Medicine, San Francisco, Calif.

When the kidneys of rats, mice, guinea pigs or rabbits are exposed under anesthesia the intravenous injection of serotonin causes a visible blanching of the kidneys. In normal rats the ED_{50} for this effect is 0.007 mg. of serotonin base/100 gm. of body weight. This reaction is inhibited by 1-hydrazinophthalazine. Intra-arterial injections of india ink during the renal blanching indicate that the ischemia occurs chiefly in the cortex. The intravenous infusion of 1 mg. of serotonin per hour for five to seven hours to normal 200 gm. rats, followed by sacrifice a week later, produces patchy areas of renal cortical necrosis. The lesions resemble those found at autopsy in pregnant women who die more than twenty-four hours after the occurrence of severe abruptio placentae.

Previous work has indicated that severe grades of abruptio placentae are accompanied by escape of thromboplastic proteins into the maternal circulation. This results in varying degrees of defibrination. Platelet participation in this massive coagulation process could be expected to release relatively large quantities of serotonin. Almost all delayed deaths following abruptio placentae are due to renal cortical necrosis of a type which serotonin is capable of producing in the rat.

ELECTRON AND LIGHT MICROSCOPIC STUDY OF THE PATHOLOGIC COURSE OF EXPERIMENTAL RENAL DISEASE IN RATS. *Carolyn F. Piel,* F. W. S. Modern, L. Dong, J. Goodman and R. Moore.* Stanford Univ. School Medicine, San Francisco, Calif., and V. A. Hospital, Long Beach, Calif.

The nephrotoxic serum, prepared by sensitizing rabbits to rat kidney, produces in rats a disease of immediate onset characterized by edema, proteinuria, hypoproteinemia and hyperlipemia.

Weekly autopsied material was prepared by vital osmic fixation for electron microscopic study. Comparable material was formalin-fixed and stained with special mucopolysaccharide and routine stains. Within six hours the glomerular capillary lumina become filled with polymorphonuclear leukocytes. By three days clumps of mucopolysaccharide material are seen in the glomerular capillary lumina which by seven days seem to have become incorporated into the capillary wall. By electron microscopy this thickening of the basement membrane is observed to be a tremendous widening of the lamina densa, the middle layer of the three discernible layers of the basement membrane. Approximately half of the material has fibrin thrombi within the capillary loops in the first two weeks of the disease. Exudation into the capsular space complicates most of the glomerular capillary pathologic changes. Healing of this process results in scarring of the glomeruli.

STUDIES OF THE MECHANISM OF EXPERIMENTAL NEPHROTIC HYPERCHOLESTEREMIA. *Ray H. Rosenman,* Meyer Friedman,* and Sanford O. Byers.** Harold Brunn Inst., Mount Zion Hospital, San Francisco, Calif.

The syndrome induced in rats by injection of rabbit anti-rat kidney serum closely mimics the nephrotic state occurring in humans. It has been found that experimental nephrotic hypercholesteremia, although initiated by the interaction of specific rabbit anti-rat kidney serum with the rat's kidney, is not due to failure of renal excretion of any plasma constituent. It has also been demonstrated that nephrotic hypercholesteremia is an isolated phenomenon confined to the plasma with no evidence of a total error in the body's cholesterol metabolism. Although found to be of endogenous origin, this isolated rise of cholesterol in the plasma was not found to be due to any abnormality in the rat's usual modes of (1) absorbing, (2) excreting, (3) synthesizing cholesterol or (4) to the

* Asterisks indicate members.

ability of the liver of the nephrotic rat to convert and otherwise degrade cholesterol. It is concluded that the isolated accumulation of cholesterol in nephrotic plasma is due to a "trapping" phenomenon which results in retention of cholesterol in the blood and failure of its normal egress from blood to the liver. The behavior of the total lipids parallels that of cholesterol. Other studies will be presented which suggest that the retention of lipids in the plasma may be due to the occurrence of chylomicronemia secondary to abnormal loss, neutralization or utilization of heparin or its clearing process cofactors.

LIPOPROTEIN SEPARATION BY PAPER ELECTROPHORESIS. *John E. Peterson,* Albert L. Chaney,* and Fung-Haan Hsu.* Dept. Internal Medicine and Pathology, College Medical Evangelists, Los Angeles, Calif.

A number of technics for measuring the separation of serum lipoproteins by electrophoretic means have been described. A paper medium is quite convenient and has been used throughout this study. Minor changes in temperature, humidity, buffer strength, voltage and paper are shown to modify results significantly. After electrophoretic separation, the paper strips can be colored by a number of dyes. Both protein and lipoprotein patterns are developed with appropriate staining, and relative changes can be measured by elution or by densitometric scanning. Slight variations in staining, washing and drying of the paper strips will profoundly change the patterns.

With meticulous attention to the variables in electrophoretic separation and staining, good reproducibility can be obtained with a standard error of approximately 5 per cent. With this degree of sensitivity changes in the lipoprotein pattern can be noted following meals of varying fat content, and changes in the gamma, beta and alpha lipoprotein areas can be followed.

PROTEIN METABOLISM IN THE MAMMALIAN KIDNEY. *Alvin L. Sellers,* Harald Eliasch, Jessie Marmorston and Sheldon Rosenfeld.* Inst. Medical Research, Cedars of Lebanon Hospital and the Dept. Medicine, Univ. Southern California School Medicine, Los Angeles, Calif.

It has been adequately demonstrated that plasma proteins pass the glomerular filter and are reabsorbed by the cells lining the proximal convoluted renal tubule. The magnitude of this process has been measured in the rat, employing the dye T-1824. It was estimated that in this species approximately 5 mg. of plasma protein per hour is reabsorbed.

If this material is degraded to amino acids and polypeptides by the tubule cells one might expect to find differences in the concentration of amino acids and polypeptides in renal arterial and venous blood. The concentration of amino acid and polypeptide nitrogen in plasma samples from the aorta, the renal vein and the inferior vena cava of the rabbit has been determined. It is demonstrated that there is a significantly higher concentration of amino acids and polypeptides in the renal vein than in either the aorta or the inferior vena cava. The possible implication of these findings in relation to the role of the kidney in protein metabolism is discussed.

STUDIES IN HUMAN PLASMA PROTEIN FORMATION. II. Fate of Transfused Internally S^{35}-Labeled Plasma Protein and Albumin, Compared with I^{131}-Labeled Albumin, and Plasma Protein Endogenously Synthesized from S^{35}-Labeled Amino Acid Precursors. *Sheldon Margen* and Harold Tarver.* Dept. Physiological Chemistry, Univ. California Medical School, Berkeley, Calif.

In a previous report it was shown that (1) the administration of S^{35} labeled amino acids to study albumin turnover may not be valid because of possible "re-entry" phenomenon from S^{35} amino acids arising from the breakdown of body proteins. Long biological half-lives (thirty-six to fifty-five days) were obtained. Moreover, when this method is employed, "pool size" must be estimated by other technics. (2) The I^{131} technic may be valid but the question of whether the iodine labeled material represents "normal" biologic protein remains unsettled. The apparent half-life of the iodinated albumin changes during the course of the experiment, gradually lengthening.

In order to evaluate the two preceding methods a large dose of S^{35} labeled amino acids was given to a donor. After twenty-four hours a phlebotomy was performed and the plasma separated. In one series of experiments the plasma was administered to normal individuals and the activity of the albumin fraction was determined on specimens withdrawn at intervals. In the other experiments the plasma was fractionated according to the method of Cohn

and the albumin administered to the normal recipients. The results and conclusions obtained from these experiments are as follows: (1) The curves obtained were different from either of the two previous methods. (2) After about six to eight days a single first order exponential curve is obtained with a half-life of twenty-six to thirty-one days. (3) The curves were the same whether plasma or albumin were employed. (4) The pool size can be determined directly with this technic. (5) "Re-entry" is of no consequence with this technic. (6) To date the technic described is the only valid one for measuring albumin "turnover."

INTRA- AND EXTRA-VASCULAR DISTRIBUTION OF CARBON MONOXIDE (CO) AND RADIOACTIVE CHROMIUM (Cr^{51}) IN BLOOD VOLUME DETERMINATIONS. *Reidar Wennesland, Norman Nomof, Ellen Brown* and James Hopper Jr.** Dept. Medicine, Univ. California School Medicine, San Francisco, Calif.

In simultaneous determinations of blood volume with CO and Cr^{51} the values found with CO averaged 16 per cent greater than those obtained with Cr^{51}. Animal experiments were undertaken to demonstrate whether this discrepancy is caused by extravascular accumulation of CO and to determine if possible which tissues have greatest affinity for CO. CO gas and Cr^{51}-tagged erythrocytes were given simultaneously to dogs (4 expts.) and rabbits (11 expts.), and the animals were sacrificed. The ratio CO:Cr^{51} was determined in the blood and used as the unit to which the CO:Cr^{51} ratio of various tissue homogenates was compared. A tissue ratio significantly larger than one was considered indicative of extravascular CO accumulation. Evidence of relative accumulation of CO was found in myocardium and red skeletal muscle. In the dog the average CO:Cr^{51} ratios of these tissues were 3.2 and 4.0 times the blood ratio. Corresponding values for the rabbit were 1.31 and 2.47, probably because of lower contents of myoglobin. A dog which had been perfused with saline showed 7.85 and 32.8.

In contrast, evidence of relative accumulation of Cr^{51} was found in the lung and spleen. In the lungs of dogs and rabbits the average CO:Cr^{51} ratios were 0.85 and 0.65, and in the lungs of the perfused dog 0.34. In rabbit spleen and perfused dog spleen the tissue ratios were 0.77 and 0.06, respectively.

It is concluded that CO accumulates in myocardium and skeletal muscle. Cr^{51} may accumulate in the lung and spleen because the physicochemical properties of erythrocytes are changed by the procedures used.

POTASSIUM CONTENT OF GASTROINTESTINAL SECRETIONS AND ITS RELATION TO TOTAL EXCHANGEABLE POTASSIUM. *N. J. Sweet, J. Nadell and I. S. Edelman.** Dept. Medicine, Univ. California School Medicine, San Francisco, Calif.

The gastrointestinal pool of potassium is not considered in present calculations of shifts of that ion in response to metabolic stimuli. Neither is it considered as a possible homeostatic reservoir when there are abnormal losses of potassium from the body. In this study we have measured the fraction of the total exchangeable potassium contained in the lumen of the gastrointestinal tract. Thirty-eight rabbit experiments have been performed. K^{42-43} was used to measure the distribution of exchangeable body potassium. Following administration of the isotope, samples of blood and urine were obtained and the gastrointestinal tracts, from the cardia of the stomach to the mid-transverse colon, were removed. These animals were studied after fasting periods varying from four to forty-two hours. The minimum period of isotope equilibration was twenty-one hours.

The following results were obtained: (1) Intralumenal gastrointestinal tract potassium content averaged 6.2 per cent of the total exchangeable potassium with a range of 2.6 to 9.8 per cent. (2) The partition of potassium in the gastrointestinal tract expressed as per cent of total exchangeable potassium was (a) stomach 0.6 per cent (range 0.3 to 1.3 per cent), (b) small intestine 1.2 per cent (range 0.5 to 2.3 per cent) and (c) cecum and proximal transverse colon 4.6 per cent (range 1.5 to 7.6 per cent). (3) The specific activity of gastrointestinal contents indicated that radiopotassium exchange is complete at forty hours. (4) In twelve rabbits forty-hour total fecal excretion of potassium averaged 3.3 mEq. (range 0.4 to 9.0 mEq.) and was therefore significant in some instances.

These data indicate that a significant proportion of the total body potassium pool of rabbits is within the lumen of the gastrointestinal tract and that this fraction is an additional subcompartment to be considered in body potassium distribution.

POTASSIUM WASHOUT BY ENEMAS. *Marcelle Dunning and Fred Plum.* Div. Neurology, Dept. Medicine Univ. Washington, Seattle, Wash.

The discovery of profound hypokalemia in a man with a cauda equina lesion led to the hypothesis that excessive potassium washout had occurred during enemas. Blood, urine and fecal contents were analyzed for potassium in this man and in other patients requiring either sporadic or repeated tap water enemas. As much as 250 mEq. of potassium was found in a single enema efflux. Potassium washout varied, however, from patient to patient and was as small as 0.5 mEq. in some instances. Serum potassium fell as much as 1.5 mEq. when washout potassium was large. Immediate urinary conservation failed to compensate bowel potassium loss. When contact between large amounts of enema fluid and bowel wall was prolonged, patients with neurogenic bowel dysfunction had the most potassium in their enema returns. Clinical symptoms of hypopotassemia were seen only when body stores had been depleted. Effective bowel care reduced the fluid and the time required for stool evacuation and prevented significant potassium wastage.

EFFECT OF RESPIRATORY ACIDOSIS ON THE INTERNAL DISTRIBUTION OF POTASSIUM. *B. H. Scribner,* J. M. Burnell and Kenneth Fremont-Smith.* V. A. Hospital and Dept. Medicine, Univ. Washington School Medicine, Seattle, Wash.

Several investigators, including Fenn, Abrams and particularly Keating, have demonstrated that metabolic acidosis causes hyperkaliemia by effecting a transfer of potassium out of the cells while metabolic alkalosis leads to hypokaliemia and an inward movement of potassium. Contrariwise the muscle analysis data of Darrow have been interpreted by many to indicate that acid-base imbalance has just the opposite effect on the internal distribution of potassium.

In this study respiratory acidosis was produced by allowing ten dogs to breathe 30 per cent CO_2 and 70 per cent oxygen, the pH falling to about 6.9. Ten additional dogs served as controls. Five dogs in each group had ureteral ligation just prior to the study. There was no significant change in the serum potassium level of anesthetized controls but in dogs with respiratory acidosis there was a gradual rise in serum potassium to levels of 6 to 9 mEq./L. Internal balance calculations using the chloride space demonstrated that this rise in serum potassium was due to transfer of potassium out of the cells.

Potassium loads were given intravenously to five normal dogs and to five dogs with respiratory acidosis. Eighty per cent of the potassium retained by the normal dogs entered the cells. None of the potassium retained by the acidotic dogs entered the cells.

These results demonstrate that respiratory acidosis causes a transfer of potassium out of the cells. This is similar to the transfer observed in metabolic acidosis by Keating.

STUDIES ON THE MECHANISM OF RENAL TUBULAR ACIDOSIS. *Telfer B. Reynolds and Helen E. Martin.** Dept. Medicine, Univ. Southern California School Medicine and the Los Angeles County Hospital, Los Angeles, Calif.

Three adult patients with well documented renal tubular acidosis have been studied in an effort to elucidate the mechanism responsible for the syndrome. All demonstrated low basal urinary ammonia and titratable acid excretion and a relatively constant urine pH in the vicinity of 6.5. Infusion of 10 cc./kg. of isotonic neutral phosphate solution resulted in a 15-fold rise in urinary phosphate excretion, a mean increase in titratable acidity from 16 to 130 μEq./minute and a mean drop in pH from 6.67 to 6.39. Infusion of 7 per cent $NaHCO_3$, 5 cc./kg., resulted in a rise in serum bicarbonate levels from a mean of 17.5 to 28.3 mEq./L. and an increase in tubular bicarbonate reabsorbtion from 1.7 to 2.8 mEq./minute/100 cc. glomerular filtrate. Bicarbonate excretion did not change significantly (23 μEq./minute).

In two of the patients oral administration of 2.0 mEq./kg./day of ammonium chloride produced a progressive symptomatic acidosis without appreciable increase in urinary ammonia or titratable acid excretion. However, equivalent oral doses of acid phosphate salt were well tolerated, acidosis did not progress and urinary titratable acidity increased fourfold.

The carbonic anhydrase system, as suggested by others, appeared capable of marked increase in activity under certain circumstances. Although bicarbonate excretion is increased in the basal state appropriate to the relatively high urine pH, tubular reabsorptive capacity for bicarbonate is not impaired. A method of increasing the low basal ammonium excretion has not been found. Current etiologic theories do not seem to be consistent with these data.

ROLE OF LACTIC ACID IN METABOLISM. *Douglas R. Drury* and Arne N. Wick.** Dept. Physiology, School Medicine, Univ. Southern California, Los Angeles, and Scripps Metabolic Clinic, La Jolla, Calif.

Lactic acid is ordinarily considered not as a fuel but as a breakdown product of anaerobic glycolysis that is reconverted to glucose by the liver before it is oxidized. Workers in the past have doubted that lactic acid can be oxidized directly by the muscles, although according to one view the muscles can convert it to glycogen. A study has been made of this problem in the eviscerated animal, making use of radioactive labeled lactate. It has been found that lactate is rapidly and preferentially burned to carbon dioxide by the extrahepatic tissues. In this preparation there is a high turnover rate of lactate. These results indicate that there is also a high turnover rate in the intact animal, although the concentration of lactic acid is kept low by its oxidation by the peripheral tissues and its conversion to glucose by the liver.

METABOLIC PATHWAYS OF COPPER METABOLISM. *J. P. Mahoney, J. A. Bush, C. J. Gubler, G. E. Cartwright,* and M. M. Wintrobe.** Dept. Medicine, Univ. of Utah, College Medicine, Salt Lake City, Utah.

Following the intravenous administration of radioactive copper to normal dogs, 0.6 per cent of the injected dose was recovered in the urine and 11.7 per cent in the stools during a five-day period. In dogs with the bile duct ligated, 2.8 per cent of the radioactive copper was recovered in the urine and 3.2 per cent in the stool. In dogs with the bile duct transposed to the urinary bladder, 12.3 per cent of the injected dose was recovered in the urine plus bile and 1.5 per cent in the stools. Similar observations have been made in normal human subjects except that a smaller fraction of the injected dose has been recovered in the excreta.

Following the intravenous injection of radioactive copper into human subjects, radioactivity in the plasma decreased rapidly and reached a low level within two hours. Thereafter, during the next four days there was a progressive rise in the radioactivity of the plasma.

VALUE OF GONADOTROPIN ASSAYS IN THE DIFFERENTIAL DIAGNOSIS OF MYXEDEMA. *Paul P. VanArsdel, Jr. and Robert H. Williams.** Dept. Medicine, Univ. Washington School Medicine, Seattle, Wash.

The differentiation of Simmonds' disease from primary hypothyroidism poses problems. We have studied the findings in ninety-four adult patients, who have shown documented hypothyroidism in the presence or absence of pituitary deficiency. There were thirty-five cases of primary myxedema; of the patients with Simmonds' disease, nineteen were due to a chromophobe adenoma, twelve to postpartum necrosis of the pituitary, three to a craniopharyngioma, two to an eosinophilic adenoma, one to an aneurysm of the internal carotid artery and twenty-two to pituitary failure of unknown cause. Special attention was paid to serum cholesterol levels, I^{131} response to thyroid-stimulating hormone, and urinary gonadotropin assays. In our experience adrenal response to ACTH and insulin tolerance tests were not of as much value in differentiating primary from secondary myxedema.

The serum cholesterol was significantly elevated in 71 per cent of the patients with primary myxedema but was elevated in only 13 per cent of those with secondary myxedema despite good nutritional status in a majority of the latter. As has been reported by others, thyroid I^{131} uptake averaged higher than in primary myxedema, although protein-bound iodine levels in serum were not significantly different in our two groups. In patients with secondary myxedema, thyroid-stimulating hormone, given intramuscularly 10 units per day for three days, produced elevations of I^{131} uptake to levels ranging from 21 per cent to 75 per cent without any particular correlation with the severity of the clinical picture. The urinary gonadotropin levels were of special diagnostic value in the postmenopausal females who comprised 83 per cent of our group of patients with primary myxedema and 36 per cent of those patients with pituitary deficiency not due to postpartum necrosis. Urinary gonadotropins were not present in any of thirty-seven patients with pituitary deficiency. In twenty postmenopausal women with primary myxedema, gonadotropins were found at the usual high amounts in sixteen, were present only at low levels in two and were absent in two. Because the occasional patient with pituitary myxedema may have a thyroid gland unresponsive to thyroid stimulating hormone, additional diagnostic tests, especially the gonadotropin assay, are indicated.

ASSAY OF THYROTROPIN (TSH) USING THYROID TISSUE SLICES. *John L. Bakke* and Nancy Lawrence.* Dept. Medicine, V. A. Hospital, Univ. Washington, Seattle, Wash.

Surviving beef thyroid slices were incubated for one hour in a modified Krebs' medium labeled with radio-iodide and then transferred to non-radioactive medium to measure the release of radio-iodide from the slice into the medium. Propylthiouracil, 10^{-3} M, was present in all mediums to prevent organic binding, thereby limiting the study to inorganic radio-iodide. TSH added *in vitro* to the release medium caused the slice to retain twice as much radio-iodide as did controls. Expressed as a tissue/medium iodide concentration ratio (T/M) a control level of 85.4 $\pm$ 9.67 (mean $\pm$ standard error) was increased to 147.7 $\pm$ 18.2 by 0.08 U.S.P. milliunits of TSH ($t_{61} = 17$, highly significant). The T/M response was proportional to the log-dose of TSH between 0.001 and 0.1 m.u., a range believed to include the normal human serum level of TSH.

Using a model consisting of two compartments, the medium iodide space and the tissue iodide space, the measured release of tissue radio-iodide over a four hour period permitted one to solve for the rate constants k_1, representing the release of iodide from the slice into the medium, and k_2, representing the transport of iodide back into the slice. In a preliminary experiment the control value of k_1 was 0.336 and k_2 was 0.378. TSH increased k_1 to 0.482 and k_2 to 0.820. Although TSH increased both rates, it increased uptake more than release and increased iodide flux ($k_2 - k_1$) eightfold as compared with controls.

These experiments support the hypothesis that TSH directly stimulates the iodide-collecting mechanism providing a sensitive response to TSH which may be directly applicable to human serum.

OBSERVATIONS OF SODIUM-RETAINING CORTICOID (ALDOSTERONE) IN HUMAN URINE. *Robert H. Curtis, Bernard J. Axelrad, Ben B. Johnson, and John A. Luetscher, Jr.** Dept. Medicine, Stanford Univ. School Medicine, San Francisco, Calif.

Sodium-retaining corticoid has been found in the urine of normal men, and increased amounts have been recovered from the urine of patients with reduced sodium excretion. The sodium-retaining corticoid from the urine of a patient with nephrosis has been identified as aldosterone by Neher and Wettstein. Aldosterone has not been found in the urine of patients with Addison's disease or in those subjected to bilateral adrenalectomy. The output of this hormone is apparently independent of pituitary control since a normal quantity of aldosterone is found in the urine of patients with panhypopituitarism and in those subjected to hypophysectomy. Marked restriction of sodium intake is followed by increased output of aldosterone. The basis for increased aldosterone output in patients with nephrotic syndrome, congestive heart failure, Laennec's cirrhosis or toxemia of pregnancy is being studied.

In general, increased aldosterone output is accompanied by reduced sodium excretion. In polycystic disease of the kidneys and in congenital adrenal hyperplasia, a normal or increased output of aldosterone may be accompanied by urinary sodium loss, presumably because the effectiveness of aldosterone is reduced.

CLINICAL STUDIES WITH 9-ALPHA-FLUOROHYDROCORTISONE. *R. H. Orr, V. Di Raimondo, M. E. Flanagan, and P. H. Forsham.** Metabolic Unit Research in Arthritis and Allied Diseases and Dept. Medicine, Univ. California School of Medicine, San Francisco, Calif.

In the rat and dog 9-alpha-fluorohydrocortisone (FF) has been shown by others to be approximately twenty times as potent as hydrocortisone in glucocorticoid and eosinopenic activity and three to five times as potent as desoxycorticosterone in electrolyte regulation. Potencies of the same order of magnitude have been observed in the experiments with human subjects to be presented. Balance studies in a bilaterally adrenalectomized-oophorectomized subject indicate that FF is considerably more than ten times as active as hydrocortisone in producing sodium retention. This effect is the limiting factor in systemic use of this compound in therapy. Topically applied 0.25 per cent FF acetate ointment appears more effective than 2.5 per cent hydrocortisone acetate in the treatment of certain inflammatory and allergic skin conditions. In such topical uses its advantage in superior anti-inflammatory potency may be explicited without undesirable side effects.

FF has been found to be a highly effective suppressant of adrenal cortical secretion. Since the metabolites of FF contribute negligibly to urinary 17-keto- and 17-hydroxy-steroids, the

measurement of these hormones accurately reflects adrenal function. Five to 10 mg. of FF given as an eight hour intravenous drip, or 1 to 2 mg. by mouth every six hours, markedly suppress adrenal cortical output. Studies of the pituitary-adrenal relation in normal as well as abnormal states of adrenal cortical function will be presented.

Preliminary results from a study of urinary metabolites of FF indicate that degradation and conjugation are similar to that of hydrocortisone. These findings, in conjunction with the observed high topical potency, support the conclusion that the potentiality of action affected by halogen substitution probably occurs at the cellular level in the target tissues.

CIRCULATING CONCENTRATIONS OF ADRENOCORTICOTROPHIN IN RHEUMATIC FEVER. *A. Bertrand Brill, Robert S. Ely* and Vincent C. Kelley.** Univ. Utah School Medicine, Salt Lake City, Utah.

A satisfactory determination of endogenous ACTH levels in blood has become possible only recently. Development of the adrenal ascorbic acid depletion method for assaying the ACTH content of blood has been applied in investigations with animals and more recently in clinical investigations in occasional patients. This method allows assessment of pituitary function permitting a separate analysis of the factors involved in the pituitary-adrenal glands. In the present study endogenous ACTH activity was determined in the blood of forty children. These included normal control groups, subjects in various stages of rheumatic fever and its therapy and patients with Sydenham's chorea. In the group of normal children, ACTH concentrations were not detectable. In rheumatic fever patients, before administration of hormone therapy, high levels of circulating ACTH were found which varied with the acuteness of the disease. Subsequently these levels were influenced by the type of therapy administered.

ERYTHROCYTE CARBOHYDRATE METABOLISM IN HEREDITARY HEMOLYTIC ANEMIAS. *A. G. Motulsky, B. W. Gabrio,* J. Burkhardt and C. A. Finch.** Dept. Medicine, Univ. Washington, Seattle, Wash.

Most hereditary hemolytic anemias are characterized by non-specific morphologic red cell anomalies. Abnormal shape may be absent altogether, as in hereditary non-spherocytic hemolytic disease. Structural changes fail to explain increased destruction in most instances. Since glucose is the prime source of energy of the red cell, an investigation of carbohydrate metabolism of abnormal erythrocytes appeared desirable. Methods included measurements of erythrocyte glycolytic rates, P^{32} uptake and analysis of non-radioactive and tagged phosphorylated intermediates by differential hydrolysis and by paper electrophoresis and chromatography. Radioautographs of paper strips allowed ready screening, visualization and densitometric quantitation of metabolic abnormalities.

Total P^{32} uptake and glycolytic rates of mature cells were normal in hereditary nonspherocytic hemolytic disease and in hereditary spherocytosis as well as in all other hemolytic anemias studied. Disturbed intracellular distribution of phosphorylated intermediates was detected in several cases of hereditary nonspherocytic disease and in hereditary spherocytosis. In the former condition, increases of 2,3-diphosphoglycerate were found, while the defect in hereditary spherocytosis consisted of accumulation of intraerythrocytic inorganic phosphate during incubation with P^{32}. Glucose and adenosine *in vitro* corrected the latter abnormality. The abnormal pattern showed little intrafamilial variability but differed from family to family.

Incubation of hereditary spherocytes for twenty-four hours at 37°c. causes marked increases in osmotic fragility. Such a metabolic stress test demonstrated the biochemical defect in another manner since glucose, adenosine and related nucleosides tended to correct the abnormal fragility.

These studies demonstrate the existence of apparently genetically controlled metabolic lesions in abnormal red cells. It has been shown that a reversible erythrocytic defect produced by red cell storage seriously interferes with viability of normal stored cells. It is suggested that the demonstrated lesions in hereditary hemolytic anemias may similarly be significant in producing the shortened red cell life span of abnormal cells.

DESTRUCTION OF BOVINE ANTIHEMOPHILIC FACTOR BY A COMPONENT OF HUMAN PLASMA. *Theodore H. Spaet* and Evelyn J. Garner.* Stanford Univ. School Medicine, San Francisco, Calif.

Although the antihemophilic factor (AHF) of human plasma is storage-labile, bovine AHF is

stable even after prolonged periods of storage. The difference between human and bovine AHF lability could be due to intrinsic differences in the protein molecule, a destructive factor in human plasma, or a protective factor in bovine plasma. To determine which of these hypotheses was more likely, AHF assays were done on mixtures of human and bovine plasma which had been incubated together at room and refrigerator temperatures. Control assays were undertaken on these same plasmas which had been incubated separately and mixed just prior to testing. Additional control assays were done on mixtures of plasmas incubated with saline. AHF was measured both by the thromboplastin generation test and by the ability of a specimen to improve the prothrombin consumption of hemophilic blood.

The AHF content of bovine plasma incubated with human plasma was lower than that of bovine plasma incubated with saline. Fresh mixtures of bovine and human plasma which had been incubated separately were as active or more active than bovine plasma incubated with saline. These data indicate a component in human plasma which destroys bovine AHF. Additional studies were made on the properties of this component. It appeared to be in fraction III of Cohn, was not destroyed by heating to 56°C., was not adsorbed on barium sulfate and was less active in serum than in plasma. Plasma from patients with hemophilia or with a circulating anticoagulant did not have greater than normal destructive activity. The data suggest that human AHF is unstable because of a plasma component which destroys or inactivates the protein.

CAPACITY FOR LEUKOCYTE AND PLATELET PRODUCTION AS STUDIED BY LEUKOPHERESIS. *C. G. Craddock, Jr.,* S. Perry and J. S. Lawrence.** Univ. California School Medicine, Los Angeles, Calif.

A technic of rapid mechanical removal of leukocytes and platelets from peripheral blood, termed leukopheresis, has been applied to dogs. Clearance of these elements at a rate in excess of one blood volume per hour for two to three hours results in marked leukopenia and thrombopenia. The reappearance of cells follows a fairly uniform pattern. For one to two hours after a single sustained leukopheresis the white cell level remains low. Steady, linear rise then begins, reaching baseline in four to five hours and continuing to 200 per cent to 400 per cent above baseline where it remains for two to three days, slowly declining to normal.

Repeated leukophereses on successive days indicate that the normal animal can rapidly replenish the peripheral blood with leukocytes even though several times the number in the peripheral blood are removed. Following three days of leukopheresis the white blood cell level rises to a peak of 30,000 to 50,000/mm.^{3} on the fifth to sixth day. The marrow changes indicate myeloid hyperplasia and immaturity beginning on the third to fourth day becoming extreme on the fifth day. Dogs exposed to heavy irradiation one hour prior to leukopheresis can still develop a leukocytotic response, although to a limited degree. This response becomes progressively less as the marrow decreases in cells.

Thrombocytopenia induced by rapid clearance of these elements from the peripheral blood persists for three to four days, with megakaryocytic hyperplasia.

IN VIVO LIFE SPAN OF LEUKOCYTES OF LEUKEMIC PATIENTS AS MEASURED BY RATE OF INCORPORATION OF P^{32} IN DNA FRACTION. *Demetrios A. Rigas and Edwin E. Osgood.** Div. Experimental Medicine, Univ. Oregon Medical School, Portland, Ore.

P^{32} is incorporated into DNA only when a cell divides. The rate of this incorporation may be used to determine the life span and the intermitotic interval of the cells. Ten patients with chronic granulocytic, eight with chronic lymphocytic, two with acute lymphocytic and three with subacute monocytic leukemia were given intravenous injections of inorganic P^{32} and daily booster injections to keep the plasma level constant. Daily blood samples were obtained, the leukocytes were separated by the phytohemagglutinin technic, the DNA was isolated by the Schmidt-Thannhauser method and its phosphorus and P^{32} determined. The DNA specific activity expressed as the per cent of that of the plasma was plotted against time and the curves were analyzed with the aid of equations derived theoretically. With adequate data these equations yield the life span and the intermitotic interval separately. However, from our data only their sum could be derived. This was found to be 5.08 $\pm$ 1.12 days for the chronic granulocytic, 4.07 $\pm$ 0.41 days for the subacute monocytic, 4.35 $\pm$ 1.46 days for the acute lymphocytic, and, in high contrast, 84.2 $\pm$ 32.0

days for the chronic lymphocytic leukemias. An analysis of variance disclosed no significant difference at the 5 per cent level among the first three but the difference in the chronic lymphocytic is obviously highly significant.

It is interesting that the figure of 5.08 ± 1.12 days for chronic granulocytic leukemia is not significantly different from that of 106 hours derived by Osgood from marrow culture data.

COMPARISON OF RELATIVE RATES OF FORMATION OF NEW LEUKOCYTES IN MYLERAN TREATED AND UNTREATED PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA: Measured by Uptake of Radioactive Phosphorus in Isolated Desoxyribonucleic Acid. *Jonah G. Li,* M. E. Leonard and Gerald Harrison.* San Francisco, Calif.

A comparison has been made between the relative rates of formation of new leukocytes in patients with untreated chronic granulocytic leukemia and in patients with the identical disease but treated with myleran (1,4-dimethylsulfonyloxybutane). The Osgood technic (Cancer, 5: 331, 1952) of measuring the uptake of radioactive phosphorus (P^{32}) in the isolated desoxyribonucleic acid (DNA) was utilized as an index of the relative rates of formation of new leukocytes.

It was found that myleran, given to four patients with chronic granulocytic leukemia in a dose of 100 mg. divided over a four-day period, suppressed the P^{32} uptake by the leukocyte DNA to approximately 20 per cent of that obtained in the untreated patient. In a single patient with chronic granulocytic leukemia treated with a lower dosage of myleran, 2 and 4 mg. on alternate days continuously, the P^{32} uptake by the leukocyte DNA was reduced to approximately 35 per cent of that of the untreated level. These findings are interpreted as indicating that myleran is effective in lowering the number of circulating leukocytes by virtue of a cytostatic action (inhibition of mitosis). It is felt that if its action were primarily cytotoxic there would be essentially no suppression of P^{32} uptake by the DNA.

CLINICAL EVALUATION OF ADMINISTRATION OF 6-MERCAPTOPURINE, 6-THIOGUANINE AND AZASERINE IN ACUTE AND CHRONIC LEUKEMIA. *B. E. Hall,* F. M. Willett, E. B. Reed, W. F. Dowling and T. V. Feichtmeir.* San Francisco, Calif.

During the past eighteen months thirty-nine patients with acute leukemia, six patients with chronic granulocytic leukemia and one patient with chronic lymphocytic leukemia have been treated with 6-mercaptopurine alone or in combination with 6-thioguanine or azaserine. Of the thirty-nine patients with acute leukemia (five children and thirty-four adults) eight received an inadequate trial of therapy. Of the thirty-one patients receiving adequate therapy, remission was induced initially in nineteen patients (61 per cent). In four adults remission was complete, lasting fifteen, twelve, six and three months, respectively. No treatment was given during complete remission. Two of the four patients are still living and well; two relapsed and died.

Of fifteen patients in whom partial remission was induced, maintenance therapy frequently was utilized. Five patients became resistant to the administration of 6-mercaptopurine alone. In two, remission was obtained by combination therapy (6-mercaptopurine and azaserine); three failed to respond to the simultaneous administration of 6-mercaptopurine and azaserine or 6-mercaptopurine and 6-thioquanine.

Details of dosage schedules, survival times, complications of treatment and biochemical studies relating to urinary excretion of uric acid, amino nitrogen, phosphorus, and so forth in acute leukemia will be presented. The results of treatment in seven patients with chronic leukemia was discussed.

BERNHEIM'S SYNDROME: IS IT A CLINICAL ENTITY? *Arthur Selzer,* Herbert W. Bradley and Forrest M. Willett.* Medical Service, V. A. Hospital and Dept. Medicine, Stanford Univ. School Medicine, San Francisco, Calif.

In the past decade there has been a revival of interest in the concept of isolated right ventricular failure appearing in the course of left-sided cardiac lesions thought to be due to deviation of the cardiac septum to the right resulting in "right ventricular stenosis" (Bernheim, 1910).

A study of circulatory dynamics was made of a patient who fulfilled all the clinical criteria for "Bernheim's syndrome," the postulated findings of which were confirmed at autopsy. It was found that the patient had marked elevation of left atrial pressure and pulmonary hypertension in addition to signs of right ventricular failure. These findings are inconsistent with the traditional concept of Bernheim's syndrome for they point to the conventional chain of events of left ventricular failure—pulmonary hypertension—right ventricular failure in spite of the clinical

absence of dyspnea and signs of pulmonary congestion. A further scrutiny of the Bernheim concept revealed that its pathologic criterion is based on a misconception, because a "deviation" of the septum encroaching on the cavity of the right ventricle can be demonstrated in all cases of left ventricular hypertrophy, regardless of the clinical pattern, and is frequently present in normal hearts. It is concluded that "Bernheim's syndrome" is not a clinical entity but merely represents a variant of conventional cardiac failure in left ventricular lesions in which the stage of left ventricular failure is clinically inconspicuous.

EARLY SYSTOLIC CLICK OF THE PULMONARY ARTERY. *Herbert N. Hultgren and John J. Kelly, Jr.* Dept. Medicine, Stanford Univ. School Medicine and State Univ. New York College Medicine, New York, N. Y.

In occasional patients with pulmonary hypertension a sharp sound closely following upon the apical first sound is present at the pulmonic area. This has been termed the semilunar opening click by Wolferth although it may not be of valvular origin. Twenty-five patients exhibiting such early systolic clicks have been studied clinically and by phonocardiography to investigate further the characteristics and mode of production of this sound. In addition cardiac catheterization and electrokymographic studies have been made to relate the time of occurrence of the click to the mechanical events in the right portion of the heart.

All patients studied had severe pulmonary hypertension, and in eight cases this was associated with an atrial septal defect. The click was maximal over the pulmonic area in the majority of cases, and it occurred from .04 to .09 seconds (mean .07 seconds) after the apical first sound. At the third interspace along the left sternal border it often resembled a split first sound but the second component was loud over the pulmonic area and faint or absent at the apex. The first sound-click time is related to the duration of the isometric contraction time of the right ventricle. The click occurs simultaneously or a brief instant after the rise of pressure in the pulmonary artery at the time when the wall of the pulmonary artery is being most rapidly tensed. These observations are in accord with those reported by Leatham and Vogelpoel in 1953.

When the sound is present and is widely separated from the first sound it is a reliable indication of severe pulmonary hypertension.

DISCREPANCIES BETWEEN SUBJECTIVE AND OBJECTIVE EVALUATION OF MITRAL COMMISSUROTOMY. *Gordon G. Bergy and Robert A. Bruce.** Univ. Washington, Seattle, Wash.

Clinical observation has revealed limited and gradual improvement as well as recurrent complications in many patients submitted to mitral commissurotomy. This experience is contrary to some of the enthusiastic reports of surgical treatment of mitral stenosis. In addition, some patients report improvement in symptoms which is not confirmed by disappearance of signs of rheumatic heart disease and its complications. In order to evaluate this confusing situation a group of thirty unselected patients have been restudied from four to thirty-eight (mean twenty-one) months after surgery. Histories were reviewed with respect to symptoms, present capacity for work and recreation, limitations of physical activity including need for daily rest periods and drugs used in continued medical treatment. Physical examination was supplemented by careful chest fluoroscopy, electrocardiogram, vital capacity and circulation time. Tolerance for a standard exercise test was determined and compared with serial preoperative and postoperative tests.

Twenty-nine patients claimed marked subjective improvement. Three were unable to work, three were working part time and three had easier jobs than before surgery. Many who claimed to be entirely well were not able to meet the requirements of ordinary daily life. Whereas five participated in sports, one-third were unable to participate in any recreational activity. Four showed signs of frank congestive heart failure when re-examined. Only thirteen patients had normal exercise tolerance. Subnormal performance was usually due to impaired respiratory efficiency (associated with low vital capacity and 0.5 second expiratory volume) and tachycardia. Four patients exhibited impaired endurance.

It is concluded that there are appreciable discrepancies between subjective and objective evaluation of mitral commissurotomy. Much of limited improvement by objective criteria relates to subnormal pulmonary function.

THE PATH OF EXCITATION IN CLINICAL AURICULAR FLUTTER. *David L. Bruns and David A. Rytand.** Dept. Medicine, Stanford Univ. School Medicine, San Francisco, Calif.

Circus movement as a hypothetical mechanism responsible for human auricular flutter seemed to be supported by the observation that, with this arrhythmia and without quinidine, the auricular rate is distinctly slower than usual in certain patients with great auricular enlargement.

Exploration of the excitation wave in two such cases by means of electrodes in the esophagus and on the anterior portion of the chest wall suggests that the long auricular cycle is related to increased path length rather than to slow velocity. The wave appeared to ascend posteriorly and to descend anteriorly as if returning. Apparent intrinsicoid deflections were recorded near the xiphoid as late as 50–75 per cent of the cycle length, timed by waves low in the esophagus within the phase alleged to represent repolarization. In one patient with a cycle length of 0.33 seconds the wave was found to be primarily negative at the manubrium (0.15 seconds) as well as at the lower esophagus (0.00 seconds) and from configuration alone might have commenced near either site; it was positive near the xiphoid (0.25 seconds). In the second patient the cycle length was 0.34 seconds; the wave was negative low in the esophagus (0.00 seconds) but positive at the manubrium (0.12 seconds) as well as at the xiphoid (0.18 seconds).

In a patient with normal auricular size and flutter at a more usual rate (cycle 0.25 seconds) the wave also was found to be negative low in the esophagus (0.00 seconds), positive at manubrium (0.05 seconds) and xiphoid (0.12 seconds). Similar observations suggesting circus movement have been reported by others.

HYPOPHYSECTOMY IN PATIENTS WITH DIABETIC VASCULAR DISEASE; CLINICAL AND METABOLIC OBSERVATIONS. *Laurance W. Kinsell,* Lester Lawrence and Robert D. Weyand.* Dept. Medicine and Neurosurgery, Samuel Merritt Hospital and Inst. for Metabolic Research of Highland Alameda County Hospital, Oakland, Calif.

In these institutions more than a year has elapsed since the first hypophysectomy was performed in a patient with malignant diabetic vascular disease. On the basis of experimental observations and observations in patients with Sheehan's syndrome superimposed upon diabetes mellitus, it was predicted prior to surgery that hypophysectomy would transform severe insulin-resistant diabetes to mild insulin-sensitive diabetes and would result in significant decrease in hypertension. It was hoped that by removal of the pituitary and adrenocortical hormones and amelioration of the diabetes, progression of the vascular disease would be slowed or stopped and that possibly improvement in lesions which were still potentially reversible might occur.

Five patients have been hypophysectomized. One of these has been re-operated upon because of a less than total hypophysectomy at the time of the first operation. There has been no operative mortality. The first two patients had extensive renal damage and died three and one-half and four and one-half months after surgery, respectively, essentially as the result of renal insufficiency. All patients have had striking increase in insulin sensitivity and disappearance of hypertension when the latter was present.

In the surviving patients, on the basis of evaluation of the optic fundi, of renal function and of albuminuria, there appears to be good reason to believe that progression of the pathologic vascular condition has been halted. Evidence strongly suggests improvement in some of the existing pathologic vascular conditions.

It is of interest that total adrenalectomy done in similar patients (personal communications from Halmi and from Conn) fails to cause any major decrease in insulin requirement. This suggests that the non-ACTH pituitary "diabetogenic factor" is chiefly responsible for the relative insulin resistance in these patients.

CLEARANCE OF RADIOACTIVE IODINE FROM THE EXTREMITIES IN PATIENTS WITH MYOCARDIAL INFARCTION. *F. K. Bauer,* F. R. Mugler, Jr., V. M. Lieberman and J. P. Westergart.* Radioisotope Unit and Medical Service, Wadsworth Gen. Hosp., V. A. Center, and Dept. Medicine, Univ. California Medical Center, Los Angeles, Calif.

It has been previously shown that tracer amounts of I^{131}, Na^{24} and K^{42} in small amounts of normal saline solution can be used interchangeably in clearance tests from injection sites. It has also been shown that clearance determinations after needle injection do not give reproducible results but that jet injection does. Tracer amounts of one microcurie I^{131} in 1 ml. sterile normal saline were injected by hypospray into the thighs and arms of healthy control subjects and of thirty-five patients with myocardial infarction. All subjects were in the supine position. The solution penetrates into the muscle. The disappearance of the injected substance is

measured with a scintillation counter which is held over the injection site. The time required for half of the radioactivity to disappear from the injection site in normal controls is from seven to fourteen minutes, with a mean of nine minutes.

It is believed that the local isotope clearance is an index of the state of the capillary bed. Two different observations are presented in support of this belief: (1) A patient with coarctation of the aorta with absent pulsations in the lower extremities had a normal clearance time in the arms and a threefold prolongation of the clearance time in the legs. (2) Two healthy control subjects received intravenous infusions of norepinephrine which more than doubled their clearance times.

None of the thirty-five patients with myocardial infarction had clinical signs and symptoms of congestive failure. The venous pressures were within normal limits as were their circulation times (Decholin). Greatly prolonged clearance times were found in these patients for several weeks and even months following myocardial infarction. Some patients received norepinephrine (Levophed) early in the study; their peripheral tissue clearances were delayed.

After the peripheral clearance in the supine position had returned to normal it was found, when some of the patients were placed in the sitting position, that the clearance times again became greatly delayed. This is not found in normal controls. This phenomenon of postural change is present both in the legs and arms but not invariably in the same patient.

It is believed that the delayed clearance of peripherally injected I^{131} in patients with myocardial infarction is caused by a diminution of the peripheral capillary bed. Whether this phenomenon is mediated through a reflex or a humoral mechanism is now under investigation.

MAXIMUM EXPIRATORY FLOW; A BEDSIDE PULMONARY FUNCTION TEST. *John R. Goldsmith.* Dept. Medicine, V. A. Hospital, Univ. Washington, Seattle, Wash.

The maximum breathing capacity test (MBC) has become accepted for measuring ventilatory function. Being arduous for the patient, and technically difficult to perform, the MBC test has been supplanted in some laboratories by timed vital capacity tests. All such tests depend on the maximum flow rate of air during expiration. Measurement of this rate has been undertaken, and its significance as a measure of ventilatory capacity is assessed. A simple, rugged, indicating flowmeter has been designed with a linear response to flow rates up to 200 liters per minute (± 3.9 L./minute). It has been used in tests on normal subjects and in patients with various types of pulmonary insufficiency. Even in advanced disease a reliable measurement may be made by taking a sufficient number of observations. The validity of tests with this portable instrument has been compared with simultaneous measurements on a sensitive, high speed, recording flowmeter during the maximum expiratory flow maneuver. The relationship of determinations by these two methods is discussed.

The correlation between maximum expiratory flow and maximum breathing capacity in forty-four patients with varying degrees and types of pulmonary disease is shown to be greater than $+.79$, confirming the validity of the maximum expiratory flow as a test of the obstructive component in pulmonary insufficiency. Its performance is as simple as a measurement of vital capacity and as easy to reproduce. Together with the vital capacity it provides a comprehensive description of ventilatory capacity.

PREGNANCY: A FACTOR RESPONSIBLE FOR BIOLOGIC FALSE POSITIVE REACTIONS AS DETERMINED BY THE TREPONEMA PALLIDUM IMMOBILIZATION TEST. *Charles M. Carpenter,* Ruth A. Boak, James N. Miller, Helene E. Drusch, John M. Chapman and Gerald A. Heidbreder.* Dept. Infectious Diseases, School of Medicine, Univ. California, Los Angeles City and Los Angeles County Health Dept., Los Angeles, Calif.

Positive standard serologic tests for syphilis (STS) in the absence of clinical evidence of the disease presents a difficult diagnostic problem. With the development of the Treponema pallidum immobilization (TPI) test, however, a valuable procedure has become available for differentiating biologic false positive (BFP) reactions from those due to infection with T. pallidum. Because of the high percentage of BFP reactions observed among pregnant women with positive STS, a study was made to determine if pregnancy *per se* is a factor responsible for non-specific reactions. TPI tests were completed in sera from 400 pregnant and 400 non-pregnant women with positive STS. Two hundred eighty-four or 71 per cent of the pregnant women as compared to only 244 or 61 per cent of the non-pregnant women gave negative TPI reactions. Thus the number of

negative results in the pregnant group exceeds those in the non-pregnant group by 10 per cent, a statistically significant difference. In order to rule out possible primary syphilis at the time of the initial negative TPI result, second samples were submitted approximately three months later. Results varied in only one case in which an initially doubtful TPI test subsequently became positive.

Standard serologic tests for syphilis were performed on the same serum sample in 169 of the pregnant women who gave negative TPI results. Ninety-seven still gave positive reactions in one or more of the tests, and sixty-six had reverted to negative results. Anticomplementary reactions were obtained only in six specimens. The standard serologic tests for syphilis on serum from 295 pregnant women in whom the TPI gave negative results indicated a low degree of specificity for the serologic tests for syphilis.

DIAGNOSIS OF POLIOMYELITIS BY TISSUE CULTURE. *William M. M. Kirby* and Charles A. Evans.* Dept. Medicine and Microbiology, Univ. Washington School of Medicine, Seattle, Wash.

Utilizing trypsinized monkey kidney cells, stool specimens from more than sixty patients admitted to King County Hospital since July 1954, have been tested for the presence of poliomyelitis virus. Virus has been recovered from more than 80 per cent of the paralytic cases and from approximately 30 per cent of the non-paralytic cases. Of special interest are (1) the occurrence of an unusually large number of type III (Leon) infections and (2) the recovery from at least six patients of viruses which are not neutralized by any of the three types of poliomyelitis antisera.

IN VITRO SUSCEPTIBILITY OF PROTEUS TO ANTIBIOTIC AGENTS. *William L. Hewitt,* Charles B. Stone and Sidney Finegold.* Los, Angeles, Calif.

The pattern of antibiotic sensitivity of approximately 100 strains of proteus isolated from clinical sources has been studied employing a serial dilution technic. Accepting the fact that the sensitivity of proteus to any agent is not of a high order, two large groups have been delineated, (1) a penicillin-sensitive, broad spectrum antibiotic-resistant group (6 per cent of the strains in this group were sensitive to chloramphenicol but resistant to tetracycline) and (2) a penicillin-resistant, broad spectrum antibiotic-sensitive group. The relation of species classification to antibiotic sensitivity classification will be discussed. On a weight basis chloramphenicol was more effective than tetracycline. Fifty three per cent of the strains were sensitive to 12.5 μg. per ml. or less of the former agent and 19 per cent of the latter. Tetracycline was as effective or more so than oxytetracycline in all instances. Only 4 per cent of the strains were sensitive to neomycin or to streptomycin.

Because of the relative resistance of these bacteria to single agents, *in vitro* studies with combinations of antibiotics were undertaken. If one-fourth or less of the effective concentration of each single antibiotic would prevent growth when combined, a significant additive effect was assumed to occur. Among the penicillin-sensitive strains significant additive effects were observed with combinations of penicillin-neomycin (90 per cent of strains) and with chloramphenicol-neomycin (77 per cent) in spite of the relative resistance to neomycin alone. In many instances the increased antibacterial effect was quite striking. Among the penicillin resistant strains significant effects were observed with tetracycline-neomycin (83 per cent) and with chloramphenicol-neomycin (60 per cent).

PROTEOLYTIC ENZYME INHIBITION. *Frederic C. Moll.** Univ. Washington School Medicine, Seattle, Wash.

The proteolytic enzyme extracted from white blood cells is inhibited by serum. The variations in this serum inhibitor have been studied in Macacus rhesus monkeys. During control periods the serum inhibitor level is constant and of low magnitude. Upon stressing the animal by a sterile abscess, the inhibitor level promptly rises during the period of inflammation. A similar rise occurs following the administration of hydrocortisone followed by a slow fall to within normal limits. In adrenal insufficiency produced by sudden cessation of cortisone therapy, the sterile abscess is not followed by rapid rise of the serum inhibitor as under normal circumstances.

These observations suggest that the level of white cell proteolytic enzyme inhibitor level in serum is controlled in part through adrenal hormones and that it responds quickly to stress in the normal animal. This inhibitor response may explain in part the anti-inflammatory action of cortisone.

EFFECT OF ANTIBIOTICS ON INTESTINAL ABSORPTION OF VITAMIN B_{12} IN DISORDERS OF THE GASTROINTESTINAL TRACT. *James A. Halsted,**

Marian E. Swendseid, Marvin Gasster and Peter M. Lewis. Los Angeles, Calif.

By subtracting the fecal radioactivity, determined with a scintillation counter, from the amount present in a test dose of cobalt^{60}-labeled vitamin B_{12} administered orally, intestinal absorption of this vitamin can be determined with reasonable quantitative accuracy. The effect of various agents on absorption, such as intrinsic factor preparations or antibiotics, can be measured.

Using a test dose of 0.5 μg. of Co^{60}-B_{12} the average amount absorbed in eleven normal individuals was 68 per cent. In ten patients with various diseases of the small intestine 24 per cent was absorbed. In eight patients with pernicious anemia and in twelve patients who had had total gastrectomies there was essentially no absorption. Concomitant administration of intrinsic factor with the test dose had no effect in normal patients nor patients with small intestine disease, but in the pernicious anemia and total gastrectomy subjects absorption became normal in each instance.

The effect of aureomycin® or achromycin® on the absorption of vitamin B_{12} was determined in six patients with pernicious anemia, in four patients who had had total gastrectomies and in ten patients with small intestine disease. Two tests were performed in each patient during the administration of two grams of the antibiotic daily.

There was no effect on absorption in any of the patients with pernicious anemia, nor in any of the total gastrectomy group. Three of the patients with small intestine disease had megaloblastic anemia associated with intestinal anastomoses and stasis of intestinal contents. In these patients a very significant increase in absorption of Co^{60}-B_{12} occurred. Of the other seven patients two had non-tropical sprue, four had regional enteritis and one had steatorrhea due to pancreatic insufficiency. Although absorption of B_{12} was impaired in each of these seven, antibiotic administration did not result in increased absorption.

The relationship of antibiotics to vitamin B_{12} utilization and to hematopoiesis will be discussed in the light of these findings.

SERUM TRANSAMINASE LEVELS IN MYOCARDIAL INFARCTION. *Clarence M. Agress,* Albert A. Kattus and John S. La Due.* Cardiovascular and Cardiology Lab., Gen. Medical Research Service, V. A. Center; the Dept. of Medicine, Univ. California Medical Center, Los Angeles, Calif., and the Sloan Kettering Inst. Dept. Medicine, Memorial Center, New York, N. Y.

Clinical studies by one of the authors (La Due) have shown that the serum level of transaminase rises significantly following acute myocardial infarction. This work indicated that a study of this kind in dogs, where varied amounts of infarction could be produced and more accurately followed, would prove valuable. The coronary arteries of thirteen closed-chest dogs were embolized with plastic microspheres. Twelve-lead electrocardiograms were used to follow the course of the infections and color photographs were taken of the hearts at autopsy. Serum samples were taken every four hours for the first twenty-four to thirty-six hours and some dogs were followed for seventy-two hours.

The results showed that in all cases the serum transaminase level rose sharply after myocardial infarction, reaching a peak between twelve to eighteen hours after embolization. There was a relatively linear correlation between the peak serum transaminase level and the amount of myocardial infarction as estimated at autopsy.

A clinical study is being carried out at the Veterans Administration Center, Los Angeles; thus far 197 determinations have been made in sixty-four patients. Eleven were controls in which the highest level was twenty-four transaminase units. A miscellaneous group, including congestive heart failure, cerebrovascular accidents, old infarcts in five patients and pericarditis in four patients were in the normal range. Peak values of thirteen patients with acute myocardial infarction ranged from 40 to 580 transaminase units. In coronary insufficiency patients, as differentiated from myocardial infarction patients, serum transaminase levels were useful in fourteen of seventeen cases.

INFLUENCE OF BLOOD TRANSFUSIONS UPON THE CIRCULATING PLATELETS IN ARTERIAL AND VENOUS BLOOD OF MAN. *H. R. Bierman,* Keith H. Kelly, and Fauno L. Cordes.* Hosp. Tumors and Allied Diseases, Div. Research, City of Hope Medical Center, Duarte, Calif.

It has been shown by Harrington et al. that the blood or plasma of patients with idiopathic thrombocytopenic purpura (ITP) infused into volunteers will cause a thrombocytopenia in the venous blood. Prompt fall in the venous platelet level within fifteen to thirty minutes after the

infusion of the (ITP) factor has been confirmed. In three of five patients, however, despite significant reduction of platelet count in venous blood, the arterial platelet number was maintained at the original level for eight hours or longer, following which both the venous and arterial platelet level returned to similar levels. Infusion of whole blood from normal donors was followed by a reduction in the number of platelets, more marked on the venous side than on the arterial side. This reduction, however, was transient and returned to normal levels within three to four hours. The reduction in number of platelets was of the order of 50,000 to 100,000 platelets per cu. mm. In the average adult there are approximately 140 to 300 billion platelets that are readily available in the circulation. The significant changes in the platelet number encountered, therefore, reflect the disappearance of massive numbers of platelets from the circulation. The site of disappearance is probably related to the peripheral capillaries and to certain viscera.

DIURNAL VARIATION OF ADRENAL CORTICAL ACTIVITY IN MAN. *V. Di Raimondo.* Metabolic Unit for Research in Arthritis and Allied Diseases and Dept. Medicine, Univ. California School Medicine, San Francisco, Calif.

Diurnal variation in adrenal activity and response has been studied in two normal males and compared with that of two patients with abnormal adrenal states; one had a single hyperplastic adrenal gland and another had been on prolonged ACTH therapy. In the normal subjects steroid determinations of 17-hydroxycorticoids (17-OHC) and 17-ketosteroids (17-KS) were made in hourly urine specimens and blood 17-OHC levels were followed at four-hourly intervals.

From the data obtained the following conclusions may be drawn: (1) The diurnal variation in total urinary 17-OHC parallels that in the blood without any appreciable lag. This appears to exclude a renal phenomenon as the explanation for the observed diurnal variation in adrenal cortical activity. (2) Variations in liver function which parallel those in adrenal function are presumably not responsible for the diurnal changes in steroidogenesis observed, a conclusion suggested by the rise in the percentage of conjugated 17-OHC during the night period. (3) A diurnal variation in the adrenal response to exogenous ACTH has been demonstrated and shown to be due to an accelerated rate of steroidogenesis when the subject was stimulated with identical amounts of ACTH in the daytime and the nighttime. This suggests that the spontaneous diurnal variation in adrenal activity is not related to changes in the endogenous secretion of conventional ACTH.

The diurnal variation was found to be present in the abnormal adrenal states studied. It appears to be due to a change in intrinsic adrenal cortical responsiveness or capacity.

Fe^{59} KINETIC TRACER DATA SIMULATION WITH THE ELECTRONIC ANALOG COMPUTER. *Oliver J. Judd and Rex L. Huff.** Seattle V. A. Hosp. and Univ. Washington School of Medicine, Seattle, Wash.

An electronic analog computer (REAC-C302) was applied to simulate the kinetics of inorganic iron in man. Plasma iron tracer data from normal subjects and polycythemia vera and aplastic anemia patients were duplicated by the computer. The model used consisted of the inorganic iron of plasma, reticuloendothelial system, storage, red blood cell precurser and red blood cells connected by suitable rate constants representing exchange between these compartments. Results indicate smaller pool sizes than expected. More comprehensive data are needed. For normal subjects rate constants and rates of red cell turnover as determined are appropriate.

The application of this modern tool to facilitate computation in determining suitability of models and pool exchange rates to explain kinetic tracer data is useful and may have many uses.

USE OF RADIOACTIVE $CHROMIUM^{51}$ AS THE ERYTHROCYTE TAGGING AGENT IN DETERMINING BLOOD VOLUME AND IN VIVO ERYTHROCYTE SURVIVAL. *Merle M. Kurtz and Harold Tivey.* Div. Experimental Medicine, Univ. Oregon Medical School, Portland, Ore.

Using radioactive sodium chromate, erythrocyte survival time and total blood volumes were determined in ten normal females and eleven normal males. The plasma volume and erythrocyte mass were calculated from venous hematocrit readings. A sample of the subject's blood was incubated with 100 μg. of $chromium^{51}$, and a washed suspension of the tagged cells was injected intravenously. Using a whole blood sample, the circulating blood volume was calculated by the isotope dilution principle. The

mean points for the volume determinations with the 95 per cent range are as follows:

	Males	Females
Blood Vol. (ml./kg.)	60 (41.8–78.2)	56.2 (44.1–68.3)
Plasma Vol. (ml./kg.)	34.1 (23.6–44.6)	34.3 (25.5–37.1)
R.B.C. Mass (ml./kg.)	25.9 (18.1–33.7)	21.9 (16.6–27.2)

Red cell survival curves, when plotted on semi-log paper, appear to follow a straight line drop to about seventy days and then a more rapid curvilinear drop occurs toward zero activity. Mathematical analysis of such curves shows promise of obtaining information which will estimate the total survival time, the elution factor and perhaps a factor of random erythrocyte destruction.

Blood volume determinations by this method have the advantage of measuring only intravascular space and offer a practical method for repeated blood volume studies over a twenty-four-hour period in the absence of blood loss. Because of the low radiation dosage to the patient blood volumes can be repeated at intervals by repeating the procedure.

INTRACAVITARY ADMINISTRATION OF TEM IN PATIENTS WITH EFFUSIONS DUE TO MALIGNANT PLEURAL IMPLANTS. *J. F. Mangum, B. E. Hall* and F. M. Willett.*

Effusions due to malignant pleural implants respond poorly to x-ray therapy and parenteral and oral chemotherapy. Intrapleural nitrogen mustard and more recently radioactive colloidal gold and chromic phosphate have been used to diminish the formation of fluid. During the past two years we have investigated the effects of the intracavitary administration of TEM in patients with pleural effusions due to lymphosarcoma, Hodgkin's disease and mesothelioma. The effect of triethylene melamine on the normal pleura of guinea pigs was studied also. This report includes three cases of lymphosarcoma, four cases of Hodgkin's disease and one case of mesothelioma with the following results: one case of lymphosarcoma with complete arrest of fluid formation for twenty-four months; one case of mesothelioma with arrest of fluid formation for eight months; one case of lymphosarcoma with definite decrease in fluid formation but no prolongation of life; three cases of Hodgkin's disease with some palliation of fluid formation but no prolongation of life, and one case each of lymphosarcoma and Hodgkin's disease with no alteration in fluid formation.

Intrapleural TEM caused no adhesions or pleural thickening in normal guinea pigs.

RACIAL AND INDIVIDUAL DIFFERENCES IN THE PERIPHERAL VASCULAR RESPONSE TO A COLD STIMULUS. *John P. Meehan.* Arctic Aeromedical Lab., Ladd Air Force Base, Alaska and Dept. Physiology, School Medicine, Univ. Southern California, Los Angeles, Calif.

Studies conducted in Alaska on groups of both white and Negro military personnel as well as on groups of Alaskan natives indicate that during immersion of the hand in ice water the Alaskan natives maintained a greater circulation to the fingers than did those subjects in the other two groups. A group of individuals who had experienced injury from the cold were similarly studied and they maintained the poorest circulation to the hand and fingers of all subjects studied. Skin temperatures as measured with thermocouples were used to indicate the magnitude of the cutaneous circulation during the exposure of the hand to ice water. Plasma volume estimations by the T-1824 method were made in all subjects studied. In general, subjects maintaining the highest skin temperatures of the hand exposed to cold had the greatest plasma volume.

A PRECIPITIN TEST FOR SERUM LIPOPROTEINS IN HUMAN CORONARY ATHEROSCLEROSIS. *Lester M. Morrison,* Monica Stevens and Hyman C. Bergman.* Los Angeles County Hosp. and College of Medical Evangelists, Los Angeles, Calif.

Recent studies by Kunkel, Gitlin, Baker and Grant and Berger have demonstrated that a simple serologic precipitin test can demonstrate the various serum lipoprotein classes in human subjects as described by Gofman. This precipitin test is accomplished by immunizing rabbits with lipoprotein fractions at Svedborg flotation rates of S_F 10–100 and S_F 10–400. The immune rabbit antiserum was then employed to detect lipoprotein concentrations in a series of forty-four human subjects (a) with proven coronary thrombosis and myocardial infarction as exemplary of atherosclerosis of the coronary arteries, (b) with seventeen so-called "normal" controls and (c) with twenty-four patients with miscellaneous diseases not affecting the cardiovascular system or disorders in lipid metabolism.

It was found that statistically significant dif-

ferences in precipitin test reactions to serum lipoproteins were found in human coronary atherosclerosis and control subjects.

CYTOLOGY OF CARCINOMA DEVELOPING IN THE GASTRIC ATROPHY OF PERNICIOUS ANEMIA. *Cyrus E. Rubin and Barbara W. Massey.* Univ. Washington School Medicine, Seattle, Wash.

Characteristic large columnar cells are shed from the gastric mucosa of patients with pernicious anemia. These cells are twice that of normal size. They are found regardless of whether or not the patient has been treated and probably reflect the severe and irreversible gastric atrophy of this disease. Most of these large cells are bland in appearance but some show morphologic indications of active growth bordering on malignancy. This is of interest since it is well established that gastric polyp and carcinoma are more frequent in this illness.

Exfoliative cytology established the diagnosis of gastric carcinoma in three elderly men who had been treated for pernicious anemia of more than twenty years' duration. Histologic confirmation was obtained by various methods, namely, gastric suction biopsy, laparotomy and necropsy. The spectrum of gastric cellular morphology was remarkably wide and varied from large bland cells through large cells of increasing activity to frank carcinoma. The morphologic evidence strongly suggested that the large columnar cell was the cancer progenitor.

This small series merits no conclusions but it poses questions demanding further study: Where do the large cells come from? Do they originate in the islands of intestinal metaplasia which dot the atrophic gastric mucosa? Will this large cell be found in certain other gastric carcinomas? Preliminary attempts to answer these questions by light, phase and electron microscopy will be described.

METABOLISM AND EXCRETION OF INTRAVENOUSLY INFUSED SORBITOL. *Victor P. Seeberg and Ernest B. McQuarrie.* Research Div., Cutter Labs., Berkeley, Calif.

We have previously observed, as have others, that intravenous administration of the hexahydric alcohol, sorbitol, causes a sharp rise in reducing substances in the blood, indicating rapid conversion to hexose. The present work was directed toward identifying the primary conversion product or products. The over-all objective is the continued exploration of the possible usefulness of sorbitol as a carbohydrate for parenteral alimentation with amino acids. Having no reducing groups, it does not participate in the Browning reaction during autoclaving and storage with the latter.

Unanesthetized rabbits were infused intravenously with sorbitol solution at constant rates and total doses approximating clinical rates and doses. Blood and urine were studied. Infused sorbitol was found to undergo considerable immediate conversion to fructose. There was also some evidence of delayed conversion to glucose. Utilization varied from 80 to 93 per cent and was dependent upon the rate of administration. Excretion consisted mainly of unchanged sorbitol with traces of reducing substances.

CHANGES IN STANDARD LEAD I OF THE ELECTROCARDIOGRAM AFTER INGESTION OF GLUCOSE. *Reider Wennesland, Rosemarie Lenel and Alfred A. Bolomey.** Cardiovascular Clinic of Kaiser Foundation Hospital, Oakland, Calif.

During a "multiphasic health check" program a number of abnormal lead I electrocardiograms were observed. On followup study many of these had reverted to within normal limits. The routine of this program involved taking the electrocardiogram one-half hour after ingestion of 100 gm. of glucose. The present study was undertaken to determine whether these "false positive" electrocardiograms might not be associated with glucose ingestion. A lead I electrocardiogram was obtained from 495 men and 499 women before and after ingestion of 100 gm. of glucose. The most common changes observed following ingestion of glucose were prolongation of the Q-T interval, lowering of the T wave, rounding of the junction and depression of the S-T segment.

In the male group the mean Q-T ratio changed from 0.964 to 0.993 with a standard error of the difference of ± 0.00215. In the female group the Q-T ratio changed from 0.991 to 1.017 with a standard error of the difference of ± 0.002. Thus in both sexes the difference of the means, 0.029 and 0.026 respectively, was thirteen times the standard error of the differences. Lowering of the T-waves was found in 27.1 per cent of the male and 33.4 per cent of the female subjects. Other changes were found in 9.9 per cent of the male and 3.8 per cent of the female subjects.

In twenty-eight males and thirty-one females

the changes led to a change of interpretation from normal to abnormal results.

INSULIN ACTION ON GLUCOSAMINE. *Arne N. Wick* and Douglas R. Drury.** Scripps Metabolic Clinic, La Jolla, and Dept. Physiology, Univ. Southern California, Los Angeles, Calif.

Insulin increases the transfer rate of glucose, galactose and mannose from the extracellular fluid into the cells of the extrahepatic tissues. Other compounds related to glucose, such as sorbitol, fructose, gluconic acid and 3 methylglucose, do not enter the muscle cells to any measurable extent even in the presence of insulin action.

In a continuation of these studies we have recently examined glucosamine, an amine derivative of glucose, which is found combined in many body constituents. This amine responds like glucose to insulin administration. Upon entering into the process accelerated by insulin, glucosamine inhibits the transfer of glucose.

EFFECTS OF ABNORMALITIES OF THE NERVOUS SYSTEM ON PERIPHERAL CIRCULATION. *Travis Winsor* and Nicholas Khoury.*

The purpose of this report is to show the effects of organic and functional abnormalities of the nervous system on peripheral circulation and to show the diagnostic value of recognizing these circulatory aberrations. The studies were carried out on 125 normal individuals and on forty-five patients with various diseases. The pneumoplethysmograph was employed to record consecutively the vasomotor reactions from one digit of each extremity. A recording thermocouple was employed to record skin temperatures of the digits and the Lang sphygmotonograph was used to record blood pressures. Certain reflexes studied were (1) the induced and spontaneous digital vasomotor reflexes recorded with the patient supine and (2) postural cutaneous vascular reflexes and systemic blood pressure reflexes recorded with the patient supine and standing. The induced vasomotor reflexes each with a different afferent nerve pathway included the inspiratory (vagus nerve), the sound-startle (acoustic nerve), the light (optic nerve) and the pain reflex (sensory nerve). The efferent pathways for these reflexes are from the medulla over the sympathetic system to the blood vessels. It was found that: (1) a lesion in one of the four receptor organs (lung, eye, ear and skin) or in its afferent pathway prevented the normal constriction of the digits of the four extremities following stimulation of the diseased organ or nerve, while stimulation of the three normal organs produced normal vasoconstriction in the digits of each extremity. (2) Lesions of the brain (medulla) resulted in an absence of vasoconstriction in the digits of all extremities when the four receptor organs were stimulated consecutively. This was seen with syringomyelia, and after reserpine and the D-H alkaloids of ergot. (3) Lesions of the upper thoracic and lumbar sympathetic ganglia (for example, quadrilateral sympathectomy) or drugs acting on the sympathetic ganglia (for example, tetraethylammonium chloride) resulted in absence of the reflexes in all digits when any one receptor organ was stimulated. (4) Localized lesions of the sympathetic nervous system in the region of the cervical or lumbar sympathetic ganglia produced localized inhibition of digital reflexes of the arm or leg, respectively, when any receptor organ was stimulated. This occurred in patients with severe diabetic neuritis and resulted in localized absence of reflexes in a digit after stimulation of any receptor organ. A posterior tibial nerve block with novocain produced similar results. In addition to the reflex changes previously described disease of the brain or peripheral sympathetic system resulted in disappearance of the spontaneous vasomotor activity which was often coincident with an increase in amplitude of the pulse waves. With disease of the brain a rise in systolic and diastolic blood pressure was not common after blowing against a 20 mm. column of mercury for 20 seconds. With localized lesions in the sympathetic system the normal fall in skin temperature of the digits (due to vasoconstriction) failed to occur when the patient stood.

Case Reports

Agammaglobulinemia in the Adult*

MARVIN ROSECAN, M.D.,† FRANK E. TROBAUGH, JR., M.D. *and* WILLIAM H. DANFORTH, M.D.
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AGAMMAGLOBULINEMIA is a unique syndrome characterized by a specific defect of a plasma protein component defined by the electrophysical pattern of the serum proteins. In recent years this defect has been discovered in several children who were subject to recurrent multiple infections.

One of the first pediatric cases of agammaglobulinemia reported was by Bruton in 1952.[1] The patient was an eight year old boy who in four years had had at least nineteen episodes of clinical sepsis in which some type of pneumococcus was recovered from his blood on ten occasions. He also had had epidemic parotitis three times. Subsequently Keidan et al.[2] diagnosed agammaglobulinemia in a fatal case of generalized vaccina in a seven week old girl. Recently, Janeway, Apt and Gitlin[3] have collected data on eight male children with agammaglobulinemia, all of whom were subject to recurrent multiple infections. These children were unable to produce circulating antibodies. The absence of serum isohemoagglutinins in patients of blood groups O, A or B served as a simple screening test for this condition. The monthly injection of 0.1 gm. per kg. of gamma globulin from the serum of a normal person gave these patients considerable protection against recurrent infections.

Other examples of "idiopathic" defects in the serum proteins, with the principal manifestation of edema due to a lowered serum albumin level, have been reported.[4–15] Lowered serum globulins were found in some of these. In the few cases studied by electrophoresis the gamma globulin has been within normal limits or considerably diminished[5–7] but never absent, and repeated infections were not apparent. In one well studied case[7] increased destruction rather than diminished production of serum proteins was noted. A decrease in gamma globulin has also been reported in patients with nephrosis[16] or malnutrition[17] with edema.

For three years we have had in our care a fifty-two year old white man with agammaglobulinemia who has experienced repeated infections of the respiratory tract and several episodes of severe diarrhea. Recently we diagnosed agammaglobulinemia in a forty year old white man who had had no difficulty with respiratory infections but had had repeated intestinal difficulties.

The authors know of eleven additional cases of agammaglobulinemia in the adult, of which four are women. Allen[18] has treated a middle-aged woman with agammaglobulinemia for eight years with several hundred plasma transfusions. During this time the patient underwent successful pregnancies. Sturgis[19] recently has observed a thirty-six year old man with this serum defect who suffered from repeated infections. Zinneman[20] has under observation three adults who have no detectable gamma globulin. One of these is a woman with granulomatous disease; an enlarged spleen has been removed. Young and Wolfson[21] have described four adult men with agammaglobulinemia and extreme susceptibility to infection, three of whom had no lymph node germ centers. Arends et al.[22] found no gamma globulin in a fifty-three year old woman who had a mild form of malignant lymphoma with repeated infections of the skin and respiratory tract. The bone marrow contained foci of abnormal lymphocytes; no plasma cells were present. Sanford et al.[23] have recently described a thirty year old house-

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wife with this abnormality which was manifested by repeated infections and a sprue-like syndrome.

CASE REPORTS

CASE 1. Patient J. N., a fifty-two year old executive, had been observed since March, 1951. Past history included a period of dermatitis on the back of his hands in 1927, followed shortly thereafter by a series of furuncles occurring periodically for five months. In 1931 he had bronchial asthma resulting from sensitivity to aspirin. In 1945 cholecystectomy was performed after an attack of acute cholecystitis. A short time later the common duct was explored because of recurrence of jaundice but no stone was found.

The first of the present infections began in January, 1950, with an eye infection for which he received three injections of penicillin. This was followed by eruptions on his face, hands, scrotum and legs, lasting two weeks. A different type of eruption then occurred consisting of small, pink, raised nodules, ½ to 2 cm. in diameter. The centers of many of these became necrotic, sloughed off, and ultimately healed, leaving small pigmented scars. Small numbers of these lesions continued to occur over the face, trunk and extremities. A course of staphylococcus toxoid and vaccine for two months proved ineffectual in controlling these lesions, but with penicillin therapy they healed completely. After administration of prophylactic penicillin, given twice weekly since July, 1950, there were only a few brief recurrences. In January, 1951, he had a severe attack of herpes zoster on the right lower flank which became gangrenous but healed with scarring. For three months prior to March, 1951, he had a cough producing small amounts of mucoid to mucopurulent sputum. He had lost 15 pounds.

When first seen in March, 1951, his temperature was 98.4°F., pulse 80, blood pressure 130/80. Other than a widespread rash as previously described, the only positive physical findings consisted of an atrophic nasal mucosa, a few rales at the posterior base of the left portion of the lung and a firm enlarged spleen descending three cm. below the left costal margin. A hemogram showed a red blood count of 5.36 million per mm.^{3}, hemoglobin 15.0 gm. per cent, a white blood count of 7,950 per mm.^{3} with a differential of 6 eosinophiles, 9 stab forms, 39 segmented forms, 42 lymphocytes and 4 monocytes. The reticulocytes were 2.2 per cent and the platelet count was 308,000 per mm^3. Urinalysis, Kahn test, fasting blood sugar test, electrocardiogram, cephalin cholesterol flocculation test and thymol turbidity test all gave normal results. Three of four stools showed occult blood. A complete examination of the gastrointestinal tract revealed it to be normal except for postoperative changes in the biliary tract and displacement of intestinal loops by the enlarged spleen. Chest roentgenogram showed honeycombing and diffuse interstitial infiltration of the left upper, left lower and right middle lobes, suggestive of bronchiectasis; fibrocalcific tuberculosis of the left upper lobe, and slight ventricular enlargement on the left side. Serum proteins contained 5.7 gm. per cent albumin and 0.2 gm. per cent globulin revealed by the methanal precipitation technic[24] and 4.8 gm. per cent albumin and 0.9 gm. per cent globulin by the salt precipitation technic. Electrophoretic analysis (Table 1) revealed no gamma globulin. A test for cryoglobulins gave negative results. Bone marrow biopsy (Table 11) showed normal cell marrow with slight erythroid hyperplasia. A quantitative plasma cell count showed only one plasma cell per 5,000 nucleated cells.[25] The tuberculin skin test gave negative results.

TABLE 1
ELECTROPHORETIC STUDIES ON SERUM

Date	Total Protein (gm. %)	Albumin (%)	Globulins (%)				A/G Ratio
			Alpha-1	Alpha-2	Beta	Gamma	
4/4/51*	....	55.3	9.7	18.0	17.0	0	1.23
4/4/52	5.01	55.3	9.8	17.5	17.3	0	1.23
11/12/52	....	54	13	19	14	0	1.17

* Made by Dr. John Taylor; the other determinations were done by Dr. S. Howard Armstrong, Jr.

The nodular rash recurred in July, 1951. Skin biopsy at that time showed slight acanthosis of the epidermis. The dermis was edematous, and in the papillary portions the blood vessels and lymph spaces were dilated. A moderate amount of perivascular infiltration of lymphocytes and histiocytes, with some polymorphonuclear leukocytes were noted. No definite diagnosis could be made.

In May, 1951, the patient had a series of acute infections of the lung and respiratory

tract (Table III). Between attacks a chronic, productive cough persisted. It is to be noted that, in spite of severe infections with high fever and at times lobar consolidation, the white blood count did not rise but usually a marked shift to the left in the differential count was noted. The

TABLE II
BONE MARROW DIFFERENTIALS

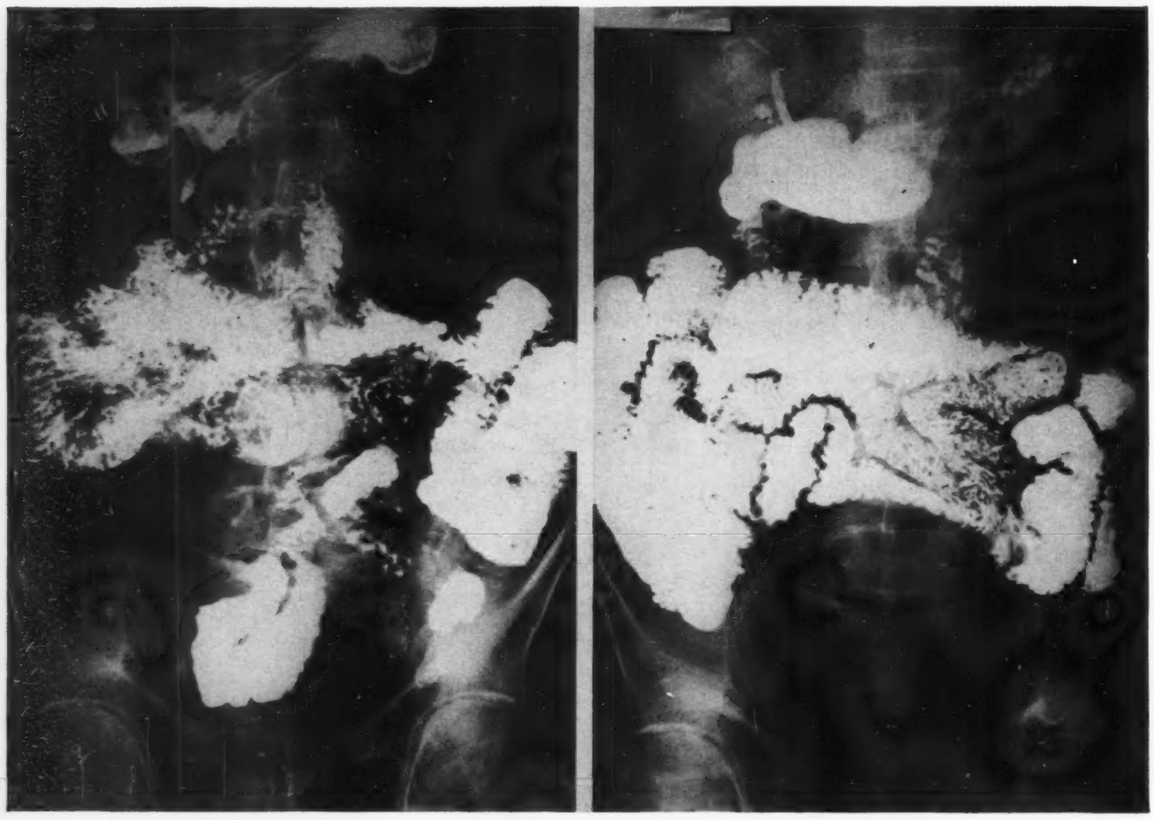
Cell Type	Patient J. N.		Patient D. S.
	March 1951	October 1953	April 1947
Megakaryocytes	1.0	1.5	1.0
Segmented forms	17.5	21	17
Stab forms	24	25.5	25.5
Metamyelocytes	10	13.5	11
Myelocyte "c"	28.5	22.5	29.5
Promyelocyte	0.5	0	0
Basophilic leukocyte	0.5	0	0
Eosinophilic leukocyte	5	0	4
Clasmatic phagocyte	0.5	0	0
Lymphocyte	9	13	10
Plasma cells	0.5	0	0
Reticulum cells	0.5	3	2
Total %	100.0	100.0	100.0
Nucleated RBC/100 WBC			
Normoblasts	54.5	81.5	42
Late erythrocytes	7.5	4	8
Early erythrocytes	1.0	4	3
Total	63.0	89.5	53

infections always responded promptly to chemotherapy and usually to penicillin alone. Physical examination revealed essentially no changes. Blood counts are recorded in Table III.

On December 9, 1951, twenty-one days after completing a course of two grams of oxytetracycline a day for six days, the patient had a sudden onset of sharp abdominal pains, fever and diarrhea with seven to ten loose watery stools daily without mucus or blood. No response resulted from administration of the usual antidiarrheal medications, and he was hospitalized on December 25, 1951. Physical examination revealed no changes except for evident dehydration. Sigmoidoscopy showed a pink, friable mucosa that bled upon slight trauma. One large ulcer was present in the anal canal. Stools contained no parasites or bacterial pathogens. Roentgenograms of the gastrointestinal tract revealed a hiatus hernia, numerous narrowed segments of small intestine with distorted mucosal pattern, and a transient jejunal intussusception. (Fig. 1A.) A barium enema gave normal results. A tentative diagnosis of acute diffuse, regional enteritis was made. While on prophylactic chemotherapy, the patient was treated for one week with ACTH, 100 mg. administered intramuscularly daily.[26] The diarrhea continued but the spleen decreased in size. Because of progressive malnutrition and debility, he was given high protein, high fat tube feeding which increased the diarrhea until there were ten to twenty bulky stools daily. He developed a hypokaliemic, hypochloremic alkalosis. On a regimen of parenteral feedings exclusively, the diarrhea subsided and the electrolyte disturbances were corrected with retention of large amounts of potassium.

During the next few weeks he was placed on a low residue diet, treated with banthine® and B_{12} injections, and in February the diarrhea gradually decreased to two or three movements daily. Studies of intestinal absorption showed a flat oral glucose tolerance curve (fasting 60 mg. per cent, one hour 102 mg. per cent; two hours 104 mg. per cent; three hours 116 mg. per cent). Fasting plasma carotene level was 34 gamma per cent (normal range 70 to 200 gamma per cent). Vitamin A tolerance showed a rise from 65 gamma per cent fasting to only 90 gamma per cent in four hours after oral administration of 300,000 units of vitamin A palmitate in oil.[27] Blood prothrombin time, calcium and amylase levels were within normal limits. The patients hemoglobin had fallen to 10 gm. per cent, and studies showed the anemia to be normochromic. Stool analysis (Table IV) showed upper normal or slightly increased fat excretion, but greatly increased nitrogen excretion.[28] Repeat roentgenographic studies of the small intestine on January 30, 1952, gave normal results. (Fig. 1B.)

Further studies (by electrophoresis (Table I) and by an immunologic technic) of the serum proteins still showed no gamma globulin. The patient's blood type was group O, Rh positive, but he had no A or B isoagglutinins in his blood. After intravenous injections of AB Witebsky substance,[29] no A or B isoagglutinins were detected. Indirect Coombs tests on the patient's serum during this period gave negative results,



1A 1B

FIG. 1. A, a roentgenogram of the small intestine taken on December 29, 1951, showed distorted mucosal patterns and irregular spacing of loops in the distal jejunum and ileum three quarters of an hour after barium ingestion. Later, films showed string signs in the jejunum. There is an intussusception near the distal jejunum which proved to be transient. Barium is seen within the common bile duct due to postoperative abnormalities. A hiatus hernia, a duodenal diverticulum and displacement of intestine due to the enlarged spleen were also present. B, a small intestinal film was taken at one and one-half hours on January 30, 1952. No abnormality of the jejunum or ileum could be demonstrated. The bladder is distended.

making unlikely the presence of incomplete antibodies. The patient's total serum complement was 77 to 50 per cent hemolytic units (simultaneous normal value was 57 to 50 per cent hemolytic units). Determination of plasma and urinary amino acids by paper chromatography revealed a normal spectrum but there were unique spots in the urine and stool which migrated in the same manner as ethanolamine conjugated with phosphoric acid.

Mild diarrhea of two to three semisolid stools a day persisted only a short time after the patient left the hospital in March, 1952. During the spring of 1952 and during the following winter he had had numerous episodes of pneumonia treated with antibiotics and divided doses of gamma globulin. (Table III.) One attack of pneumonia in November 1952 was complicated by a sterile pleural effusion which contained 7,600 red blood cells/mm.^{3}, 1,250 white blood cells/mm.^{3}, 70 per cent polymorphonuclears and a protein content of 3.1 gm. per cent.

In February, 1953, the patient again had a sudden onset of six to ten loose, watery stools a day with cramping, and the pustular skin rash on the face recurred. He lost 12 pounds. The usual antidiarrheal agents again were of no help. He was given penicillin, gamma globulin injections, banthine and cortisone, the latter in dosages starting with 200 mg. per day and gradually decreasing to 100 mg. per day. Within a week the skin rash cleared, the diarrhea subsided to two semiliquid stools daily and the patient began to regain weight.

During the next eight months he had several episodes of skin rash, sinus and pulmonary infections, as recorded in Table III, for which

TABLE III

SUMMARY OF CLINICAL COURSE (PATIENT J. N.)

Year	Month	Infection	Temp. °F	White Blood Count						N.	Treatment
				Total	Eo.	Juv.	Stab.	Seg.	Lym.		
1950	1	Eye infection	.....	.....	..	..	..	..	..	..	Penicillin
	3	Skin rash	.....	.....	..	..	..	..	..	..	Staphylococcus vaccine
	6	Cellulitis, hand	.....	.....	..	..	..	..	..	..	Penicillin
	9	.....	.....	.....	..	..	..	..	..	..	Prophylactic penicillin
1951	1	Herpes zoster	.....	....		..	..	..	..	..	.....
	2	Right flank	.....	7,200	..	..	3	66	30	1	.....
	3	.....	.....	7,950	6	..	9	39	42	4	.....
	5	Pneumonia L.L.L.	101.6	7,750	..	..	..	..	..	..	Penicillin, chlorotetracycline
	7	Skin rash	98.2	5,450	5	..	3	41	51	..	Penicillin
	9	Upper respiratory infection	97.6	9,000	4	..	..	57	38	1	Penicillin, chlortetracycline
	10	Acute bronchitis and sinusitis	102.5	5,700	..	..	..	..	..	..	Oxytetracycline, 1 week, antral washing
	11	Acute sinusitis	102	6,750	..	..	16	47	36	1	Penicillin and oxytetracycline, 1 week
	12	R.U.L. pneumonia	103	7,800	..	..	54	14	19	14	Penicillin
1952	1	Diarrhea and rash, R.L.L. pneumonia	101	....	..	..	..	..	..	..	Banthine, ACTH, etc., penicillin
	2	L.L.L. pneumonia	102	....	..	..	..	..	..	..	Penicillin
	3	R.L.L. pneumonia	101	4,950	6	..	14	43	30	7	Penicillin, chlortetracycline
	5	L.L.L. pneumonia	101	6,800	2	..	25	33	32	8	April 16–May 7, 3.2 gm. gamma globulin 1 M., penicillin, chlortetracycline
	6	.....	.....	8,100	6	3	17	26	40	8	Feeling well
	7	.....	.....	4,200	..	..	16	42	40	2	.....
	11	L.L.L. pneumonia	103	9,200	..	2	51	25	21	1	Penicillin, Nov. 12–Jan. 13, 1953, 5.42 gm. gamma globulin, penicillin + thoracentesis
	12 and 1/53	L.L.L. pneumonia w. sterile pleural effusion	101+	4,950 5,300	.. 3	.. ..	.. 15	.. 41	.. 36	.. 5	
1953	2	Diarrhea and skin rash	.....	5,800	1	..	23	45	29	2	Penicillin, cortisone, banthine, etc., Feb. 10–15, 3.8 gm. gamma globulin

TABLE III (*Continued*)

Year	Month	Infection	Temp. °F	White Blood Count						N.	Treatment
				Total	Eo.	Juv.	Stab.	Seg.	Lym.		
1953	3	Acute bronchitis and sinusitis; Friedländer's bacillus in sputum; ankle edema; local swelling of dorsum of hands	101	4,100	1	..	19	35	399	3	Penicillin, sulfadiazine, 2.3 gm. gamma globulin, March 4–19
	4	Contact dermatitis of hands and back; pustular rash of back	.....	4,300	..	..	..	..	...	..	Local therapy
	5	Acute sinusitis	100	4,100	..	..	..	..	...	..	Penicillin, triple sulfa
	7	R.L.L. + L.L.L. pneumonia; alkaligenes fecalis, Staph. aureus and hemophilus	101.8	3,900	2	..	6	8	80	4	Penicillin, streptomycin, July 25–Aug. 10, 8.7 gm. gamma globulin
	8	Type A Friedländer's bacillus	100.6	3,900	1	1	24	15	53	3	Triple sulfa, oxytetracycline
	10	R.L.L. pneumonia, alpha + beta strep, Neisseria	101	6,950	1	..	23	39	31	4	Penicillin 1.3 gm., gamma globulin, triple sulfa, tetracycline
			.....	5,150	2	1	7	47	37	6	
	11	Spleen, larger and tender	.....	5,000	2	..	22	23	50	2	Splenic puncture,
	12		.....	1,550	2	1	10	16	70	1	X-ray to spleen, 450 roentgens
1954	1	Slight cough; postnasal drip; spleen smaller	.....	4,100	6	1	24	31	35	3	From Nov. 30–Dec. 8, 3.9 gm. gamma globulin
	6	Well; spleen larger	.....	4,000	5	..	19	39	34	3	.96 gm. gamma globulin per week, Jan.–June

he received antibiotics and gamma globulin injections. During the infections of July, 1953, a transient, profound granulocytopenia was observed. In March, 1953, a non-tender tenosynovitis appeared on the dorsum of both wrists which subsided in several months.

In April, 1953, he received 500 microcuries of S-35 labeled yeast, and the albumin and globulin turnover time was determined by Dr. S. H. Armstrong, Jr.[30] The results of the test were as follows: albumin turnover time, thirty-five days; mixture of alpha$_1$, alpha$_2$, beta globulin turnover time, eight days; gamma globulin turnover time, no radioactivity recovered in the gamma portion on paper. These turnover times are either in the upper normal range or are slightly elevated.[31]

In October, 1953, the patient's spleen was tender and became larger. It extended 11 cm. below the left costal margin, and the liver edge was felt 3 cm. below the right costal margin. At that time the red blood count was 5.17 million/mm.^{3} hemoglobin, 12.7 gm. and platelets, 435,000/mm.^{3} The white blood count, the differential count and results of bone marrow examination are recorded in Tables II and III.

Blood non-protein nitrogen, fasting sugar, and liver function tests gave normal results.

He was admitted to the hospital. A splenic puncture was performed. Microscopic sections revealed atrophy of malpighian follicles, hemosiderosis, rare megakaryocytes and myelocytes,

TABLE IV
STOOL FAT AND NITROGEN EXCRETION

Period	Fat			Nitrogen		
	Intake (gm./day)	Output (gm./day)	Excretion (%)	Intake (gm./day)	Output (gm./day)	Excretion (%)
2-2-52 to 2-6-52	90	10.5	11.5	10.6	3.1	28.8
2-16-52 to 2-20-52	120	8.7	7.4	....	...	....
Upper normal values[21]	102	6.7	6.8	18.8	2.5	13.3

with questionable stem cells in the pulp and a questionable increase in reticulum cells. Because of the size of the spleen and the possible role of secondary hypersplenism in the hematologic picture, it was decided to irradiate the spleen. After 450 roentgens in eleven days, the procedure was terminated because of a granulocytopenia which proved to be self-limited. The spleen shrank to 7 cm. below the left costal margin. From December to June, 1954, he received 960 mg. of gamma globulin intramuscularly weekly without recurrence of active infection. However, a postnasal drip and a slight productive cough persisted for several months. The spleen has gradually increased to its former size.

CASE II. Patient D. S., a forty year old oil field superintendent, was first seen in 1947 when he was thirty-three years old. He had an eight-week history of severe and frequent vomiting following ingestion of food. For about a year and a half he had frequent bloating, heartburn and heaviness in his epigastrium, with occasional vomiting and intolerance to fatty foods. There had been one period of bright red blood in the vomitus. He had lost 30 pounds.

Physical examination revealed the temperature and pulse to be within normal limits. The blood pressure was 92/52. He was poorly nourished. The only positive physical observation was abdominal tenderness just above the umbilicus. None of the organs was palpable, and muscle guard was absent.

Laboratory data revealed a hemoglobin of 13.0 gm. per cent. The white blood count was 5,300/mm.^{3}; the differential blood count showed 60 segmented forms, 34 lymphocytes, 4 monocytes and 2 eosinophils. The reticulocyte count was 3.7 per cent and the platelet count was 119,000/mm.^{3} Serum non-protein nitrogen was 13 gm. per cent, fasting blood sugar 74 mg. per cent, amylase 95 units per cent, albumin 3 gm. per cent and globulin 1.2 gm. per cent. Examination of the gastrointestinal tract showed narrowing in the second portion of the duodenum approximately 8 cm. from the duodenal bulb, at which point the duodenum was only ½ cm. in diameter. It was believed this was either a narrowing due to adhesions or to an annular pancreas.

At surgery an annular pancreas was found. A number of enlarged lymph nodes were present at the base of the mesentery. Microscopic sections of the lymph nodes showed nonspecific chronic inflammation. The patient, feeling well, was discharged. He was readmitted ten days later because of three days of loose watery stools and one day of upper abdominal colic and vomiting. Bone marrow examination (Table II) revealed one plasma cell per 5,000 nucleated cells.

On admission his temperature was 37.2°C.; blood pressure was 112/60. Slight left axillary lymph node enlargement was noted. One observer thought the liver was enlarged. Laboratory study revealed the urine to be within normal limits except for an occasional red cell and white cell. His hemoglobin was 10.6 gm. per cent. The white blood count was 4,000/mm.^{3} and the differential count revealed 62 segmented forms, 1 stab form, 32 lymphocytes, 3 eosinophils and 1 basophil. Serum non-protein nitrogen was 13 mg. per cent, icterus index 5 and amylase 66 units per cent. Cephalin flocculation test gave negative results; thymol turbidity test revealed 1.2 units, and a bromsulfalein test revealed no retention in 45 minutes. Prothrombin time was 47 per cent; clotting time was six minutes; red cell fragility showed beginning hemolysis in 0.43 per cent saline solution and was complete in 0.32 per cent saline solution. Two determinations of serum proteins showed albumin to be 2.8 and 3.3 gm. per cent, and globulin to be 1.2 and 1.3 gm.

per cent. Two stools gave negative results to the guaiac test, and one stool was described as showing some increase in fat. Studies of the upper gastrointestinal tract revealed a filling defect resulting from external pressure on the antrum and the distal part of the greater curvature of the stomach. The duodenal loop was described as being partially widened but there was no obstruction in the duodenum. The proximal small intestinal loops were atypical and slightly dilated, and there was some question as to partial small bowel obstruction. A barium enema gave normal results. During this hospital stay biopsy revealed chronic inflammation of a cervical lymph node. A later review of this and the previous abdominal lymph nodes revealed absence of the germinal follicles.

The patient gradually gained weight. Blood tests showed consistently normal hemoglobin, white counts were between 4,000 and 6,000, differential counts gave normal results and the urine was normal. Sedimentation rate was 4 mm. an hour. Splenomegaly was first detected in December, 1947.

The patient was admitted for the third time on March 11, 1954, because of three days of diffuse abdominal pain with severe waves of colic every five or ten minutes. He felt better in a sitting than in a lying position; some concomitant abdominal swelling was present. His bowels moved normally. On the day before admission he vomited a great deal. His temperature was 37°C., his pulse 80 and his blood pressure 120/70. His abdomen was distended and tender throughout the right half. It was thought the patient had upper bowel obstruction and this was confirmed by a flat film of the abdomen.

Laboratory analysis revealed a hemoglobin of 14.6 gm. per cent; the white blood count was 6,600 with 69 segmented forms, 8 stab forms, 21 lymphocytes and 2 monocytes. The urine was within normal limits. A trace of albumin and 2 to 4 white cells per high power field were present. Serum non-protein nitrogen was 30 mg. per cent. Fasting blood sugar was 135 mg. per cent. Electrolytes at the time of admission showed sodium to be 143.7; potassium, 316; chloride, 95; and CO_2, 31.3 mEq. per liter. Blood albumin was 5.8 gm. per cent; globulin, 0.6 per cent.

The bowel was decompressed by a Homer-Smather tube connected to Wangensteen suction. The decompression was prompt and, except for a temperature spike to 40°C. on the third day, the recovery was uneventful. Further laboratory tests showed serum non-protein nitrogen of 21 mg. per cent on March 15, and the white blood count was 11,200/mm.^{3} with 79 segmented forms, 7 stab forms and 14 lymphocytes. The electrocardiogram, which had been previously within normal limits, now showed a right bundle branch block. A chest roentgenogram revealed no abnormalities. Examination of the upper gastrointestinal tract revealed the first part of the duodenum to be displaced upward and the third part to be displaced a little to the right. The small bowel examination revealed an extrinsic mass 6 cm. in diameter in the right periumbilical region and some displacement of the stomach consistent with splenic enlargement. A barium enema revealed no abnormalities.

Repeat blood protein studies showed an albumin of 5.0 gm. per cent and a globulin of 1.0 gm. per cent. Paper electrophoresis of the serum revealed no gamma globulin. The patient's blood was type A, Rh negative, and there were no alpha or beta isoagglutinins demonstrated. Sedimentation rate was 1 mm. per hour. The heterophile test and agglutination tests against brucella, typhoid O and H, paratyphoid A and B, and tularemia all gave negative results.

The patient was discharged in satisfactory condition. Six months later he was found to have remained well and to have been working regularly.

COMMENTS

Some of the juvenile cases of agammaglobulinemia previously reviewed may represent a congenital defect in the formation of gamma globulin, possibly sex-linked in some cases, because of the predominant occurrence in males. Patient J. N., Case 1, no doubt acquired this disease in recent years, particularly since he suffered from asthma twenty years previously due to hypersensitivity to aspirin.

Speculation as to the pathogenesis of this disease introduces controversies over the cellular source of antibodies and gamma globulin. The evidence has recently been reviewed,[32–34] and points toward plasma cells or lymphocytes as the principal sites of antibody formation. The problem is complicated by varying opinions on the development and morphology of cells. Perhaps more than one cell type is concerned.

Using quantitative bone marrow counts of plasma cells, Good and Campbell[25] have been able to correlate plasmacytosis with the elevation of serum gamma globulin in patients with rheumatic fever. The low bone marrow plasma cell count found in these patients further suggests these cells as a source of gamma globulin.

The half-life of human gamma globulin has been established as twelve to fourteen days,[35] with a somewhat longer survival in children. The long half-life of passively transferred gamma globulin in these patients[1,3] suggests that the primary defect is deficient synthesis rather than excessive destruction of gamma globulin. Paper chromatography of amino acids was carried out in an attempt to discover some specific defect in the metabolism of amino acids but the amino acid spectrum was normal. However, the observation of abnormal amounts of conjugated ethanolamine in the plasma and urine of J. N. (Case 1) suggests further investigation of the role of this substance in gamma globulin formation. Conjugated ethanolamine has also been found in the urine of premature infants who are known to be deficient in antibody formation.[36]

Cohn et al.[37] have determined that most immune antibodies and isohemagglutinins reside in the gamma globulin fraction of plasma, while the major portion of C^1 and C^2 components of complement are contained in the alpha and beta fractions of plasma, respectively. The patients here described have no isohemagglutinins and were unable to produce any, whereas the serum complement was within normal limits. The presence of a normal serum complement titer in J. N. emphasizes the secondary role that complement plays in resistance to bacterial infection. It is ineffective as a bactericidal agent in the absence of specific antibodies.[38]

The etiology of the splenomegaly and the reason for the failure of J. N. to respond to infections with leukocytosis are obscure. At one time marked granulocytopenia was present. The condition of at least one pediatric patient with agammaglobulinemia has been complicated by granulocytopenia during infections; this patient was regarded for years as having recurrent splenic neutropenia before the agammaglobulinemia was discovered.[39] Menkin[40] has isolated a leukocytosis-promoting factor from inflammatory exudate and identified this as a pseudoglobulin distributed between the alpha-1 and alpha-2 globulins of exudate.[41] It is possible that some component of gamma globulin is necessary for the elaboration of this leukocytosis-promoting factor.

Although the recurrent respiratory infections and the skin rash, apparently infectious in origin, can be attributed to the agammaglobulinemia, it is more difficult to account for J. N.'s diarrhea. The flat glucose tolerance and vitamin A tolerance, the low-fasting carotene level, the slightly elevated stool fat on one occasion and the intensification of the diarrhea by high fat feedings all serve to classify this as a steatorrheal syndrome. The large nitrogen stool is compatible with this disease, according to recent studies.[42] Tumor was suggested by the transient intussusception, but the patients' subsequent improvement noted on roentgenograms and his clinical remission speak against this diagnosis. It is also possible that oxytetracycline was responsible, even with the delayed onset. Four patients with prolonged steatorrhea following the use of antibiotics have been reported,[43] and in one of these the onset began a week after discontinuing administration of the drug. However, our patient subsequently tolerated oxytetracycline without difficulty. A plausible diagnosis is an unusual form of diffuse jejunoileitis, with the course influenced by altered response to infection. This could account for various deficiencies in intestinal absorption.[44]

Patient D. S. was unique among all patients with agammaglobulinemia reported in adults and children in that he was relatively free of repeated infections. However, inflammatory lymph node enlargement probably contributed to the first and was in large part responsible for the second episode of intestinal obstruction, which responded to conservative management.

SUMMARY

Two case studies of adult white men with agammaglobulinemia and splenomegaly are reported. One has been subject to repeated bacterial infections of the skin and respiratory tract and has had several attacks of severe diarrhea. The other patient has had recurrent small bowel obstruction probably due to inflammatory lymph node enlargement, but has otherwise been virtually free of infection.

The occurrence of this syndrome in adults is discussed.

Acknowledgements: The authors wish to thank Dr. Harry Alexander for his help and criticism in treating patient J. N. (Case I) and in the preparation of this manuscript; Dr. Richard Weiss, who first treated the skin infections and referred patient J. N. to us; Dr. S. Howard Armstrong for the special protein studies and for his helpful advice; Dr. Keith S. Wilson who diagnosed the condition of patient D. S. (Case II) and permitted us to include him in this report; Dr. Albert Mendeloff for the carotene and vitamin A determinations; Dr. Sam Frankel for the amino acid paper chromatography, Dr. David Gitlin for the gamma globulin determination by the immunologic technic and Dr. Amoz Chernoff for the paper chromatography of serum proteins.

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Bronchiolitis Obliterans*

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An infrequently described lesion, bronchiolitis obliterans, would appear to be a rare entity. The distinctiveness of the lesion makes it unlikely that it would not be recognized. It is pertinent that LaDue,[1] making a specific search, found only one case in 42,038 consecutive autopsies covering a forty-two-year period. And yet Winternitz[2] consistently found cases among dogs exposed to chlorine, phosgene, chloropicrin and other war gases. It would be anticipated that cases in human beings would have been found in large numbers after the gassing attacks in World War I. This does not seem to have been borne out. Muntsch[3] mentions bronchiolitis obliterans among the residual pulmonary effects of World War I gas poisoning but gives no indication of its frequency. It seems to have been a relatively frequent complication of the influenza pandemic.[4,5]

Since the original description of the lesion by Lange[6] in 1901—all references prior to 1949 may be found in reviews by LaDue,[1] Blumgart and MacMahon,[7] and Amoroso and McNally[8]—the scattered reports seem to justify three distinct etiologic forms of the disease: (1) following inhalation of irritant substances, (2) as a complication of pulmonary infection, (3) unknown etiology.

Fumes of oxides of nitrogen are the more common[1,7,9] of the irritant substances cited in the literature as causes of bronchiolitis obliterans. They may arise from burning nitrocellulose film, explosives, breakage of carboys of nitric acid or other containers, and from other sources.[10] The composition of the fumes will vary but some generalizations can be made.[9,10] Nitric oxide, itself non-irritating, undergoes comparatively rapid oxidation to nitrogen dioxide. From the toxicologic standpoint, nitrogen dioxide is the most important of the oxides of nitrogen.[11] It readily polymerizes to nitrogen tetroxide, existing as a mixture of approximately 30 per cent NO_2 and 70 per cent N_2O_4 at body temperature. Each is readily soluble in water and forms nitric acid which causes the lesion. Hydrochloric acid has been reported as a cause and sulfuric as well as unspecified acid fumes have been cited in a few cases. Edens reported on two patients with a typical clinical picture of bronchiolitis obliterans following exposure to acid fumes and strong ammonia, respectively, each of whom recovered.[12] One case was reported as due to a cellulose-containing furniture stain but the description leaves one uncertain that bronchiolitis obliterans is truly represented.[13] Reference to chemical warfare agents has already been made. In general, these agents have been chlorinated compounds.

Pulmonary infection has been responsible for some of the reported cases. Blumgart[7] reported a case in a boy with scarlet fever followed by pertussis, and reference is made to another unpublished case in a boy following pertussis.† The lesion was also seen as a frequent component of influenza in the great pandemic of World War I. Winternitz[4] stated that twelve of his ninety-five autopsied cases showed organization of the bronchiolar or alveolar exudate. The case of Lerfer and Winkler[14] followed a grippe-like illness. In an exhaustive study Hübschmann discusses the lesion in influenza.[5] Other infectious origins are also cited. Beitzke[15] discussed bronchiolitis obliterans as a sequel of acute (capillary) bronchitis. As a component of organizing pneumonia the lesion is probably not unusual. In such instances, however, the phenomenon is essentially a local one. This also applies to instances in which foreign bodies are concerned.

Bronchiolitis obliterans, apparently due to iodized poppyseed oil, has been reported but in the instance cited evaluation was made difficult

† This case (Autopsy No. 5-33) is from a collection of Dr. J. R. M. Innes, obtained while he was at the Institute of Pathology, Munich, under Prof. Max Borst, 1932 to 1933. (Permission of Prof. W. Hueck, Pathologisches Institut der Universität, Munich, Germany.)

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by a long standing history of respiratory disease prior to bronchography.[1] There are certain objections concerning a report of bronchiolitis obliterans associated with pulmonary vasculitis. Two of the three cases were in individuals with chronic cardiovascular disease. Several illustrations used to demonstrate vascular lesions, moreover, show altered bronchial arteries. Actually, the changes pictured are commonly noted lesions of the bronchial artery and have been specifically discussed by Liebow et al.[16]

The clinical picture[1,7,9,10,14,17] of bronchiolitis obliterans is variable at its inception, depending on its etiology. In the more common instances due to oxides of nitrogen or other irritant fumes, there is an initial period of cough, dyspnea, slight or severe chest pain and cyanosis. The patient is usually afebrile. Most fatalities occurring at this time show acute necrotizing lesions of the tracheobronchial tree and massive pulmonary edema. When pulmonary infection is the initial lesion, the symptoms correspond. There is then an interval of apparent improvement over a period of several days to a month or more, although a few cases show gradual progression. This interval tends to be short in cases due to inhalation of irritants.[18] The third stage appears to have the same clinical characteristics in all groups and is remarkable for its unremitting nature. The cases of uncertain etiology are generally first recognized in this stage.[19] Dyspnea becomes progressively and rapidly more marked, there is variable cough and expectoration of blood-stained sputum. Cyanosis is always conspicuous. There may be fever but this is generally low grade. In this third stage the roentgenogram of the chest may simulate miliary tuberculosis which may offer the main problem in differential diagnosis. The importance of this roentgenographic pattern in a patient with marked dyspnea is to be emphasized. It would be desirable to anticipate the disease before it develops but there are apparently no reports specifically demonstrating the evolution of the roentgen pattern. There are, however, reports of the changes in x-ray in acute poisoning due to oxides of nitrogen which can be taken to represent the probable early pattern of those going on to develop bronchiolitis obliterans. Soon after exposure there is an irregular, soft mottling throughout both lung fields. These patches of increased density follow the course of the bronchial tree and extend to the periphery of the lung fields,[18,20] tending to be more numerous in the mid-lung fields.[15] There is then confluence of minute areas of atelectasis and edema, with development of larger nodules. This stage is remarkable for the rapidity with which the chest film clears in those who recover.[20–22] However, the miliary-like densities may persist. In this regard Nichols'[23] experience with the Cleveland disaster (1929) from burning nitrocellulose film is of some interest. He found that while the clinical examination of the chest was often unremarkable, the roentgenogram always revealed many small nodular areas scattered throughout each lung. On the basis of preliminary autopsy findings in fatal cases, these densities were explained as being due to foci of interstitial fibrosis. However, the fact that a group of the victims showed a phase of clinical improvement followed by relapse with severe cyanosis approximately fifteen days subsequent to the exposure is strongly suggestive that these foci of "interstitial fibrosis" were actually the lesions of bronchiolitis obliterans.

Pathologically, the appearance of the gross lesion is distinctive and, if the clinical picture is known, should not be confused with miliary tuberculosis which it closely resembles.[1,7,8] The parenchyma of all lobes is studded with small nodules, generally 1 to 2 mm. in diameter, which are serrated in outline. Careful observation of the cut surface of the nodules reveals a slit-like or rounded space in the central portion of many, the remnant of the bronchiolar lumen. The latter feature is important in differentiation from miliary tubercles. Miliary lesions in other body locations are absent. Emphysema and atelectasis, singly or in combination, may be found and the lungs are frequently edematous and show focal hemorrhages. Such hemorrhage was a conspicuous feature in the experimental lesions produced by Winternitz[2] and could be correlated with the violence of the agonal state.

The descriptions of the histologic changes of the several reported cases vary, even in cases due to the same cause. It is possible that this reflects more than one mechanism in the pathogenesis of the lesion. In the characteristic lesion[1,7,15] the lumen of the bronchiole may be partially obliterated by granulation tissue. The obstructing mass often has a polypoid appearance and is separated by a space from a crescent of intact, probably regenerated, bronchiolar epithelium, or the lumen may be entirely obliterated by young connective tissue. There

is a diversity of opinion concerning the earlier stages which end in this picture. The earliest lesion is certainly an acute bronchiolitis with destruction of the epithelial lining. When irritant fumes are the etiologic factors there is probably accompanying alveolar injury. This is based on the observation that most severely exposed individuals die early with massive pulmonary edema. Extensive necrosis of the wall of the bronchiole apparently does not generally occur in these patients.[1,4,7,12] In this respect it is significant that bronchiolectasis is infrequently noted.[1] That the damage may be more than simple inflammation of the bronchiolar wall is implied by most authors who describe disruption of the muscularis and elastica. The source of the granulation tissue is generally agreed to be the wall of the bronchiole, and it is here that there is the most divergence of opinion, i.e., whether it arises in the submucosa or muscularis, represents an infiltration of peribronchiolar origin, or is a reaction of the wall as a whole.[24] Involvement of neighboring alveoli is mentioned in most reports, and it is improbable that there have been any cases in which contiguous alveolar structures were not involved. This is certainly so in cases following influenza, as pointed out by Winternitz.[4] Most authors consider alveolar involvement to be secondary to the bronchiolar involvement. However, an alveolar origin of the process leading to bronchiolitis obliterans has not been convincingly excluded.[18] Groll's excellent description clearly demonstrates the role of alveoli in the organizing process.[25]

CASE REPORT*

On December 29, 1953, the patient, a thirty-eight year old chemist employed by the U. S. Bureau of Mines, aided in the rescue of a colleague after a group of flasks containing red fuming nitric acid exploded as they were being vented. The laboratory was quickly filled with dense fumes, chiefly of nitrogen dioxide. There is little information about early symptoms other than that the patient is said to have had a cough following the accident, and had tightness in the chest the first few days. He took sick leave, unusual for him, but complained of no symptoms other than cough until January 19, 1954. The cough increased in severity and he experienced chilly sensations with fever. He consulted a physician for the first time on January 21, 1954. Only loud rhonchi were noted on examination of the chest. His symptoms became rapidly and progressively more marked, and retrosternal pain, a feeling of tightness in the chest, and later shortness of breath developed. Treatment with aureomycin was begun on January 23, 1954. The following day shortness of breath was so severe that he had to remain in a sitting position.

On admission to the hospital on January 24th, he had a dry hacking cough, dyspnea showing marked respiratory effort and a respiratory rate of 52/min. Temperature was 100.4°F., pulse 128/min., blood pressure 170.90 mm. Hg. Abnormal findings, limited to the chest, were wheezing, sonorous breath sounds and râles throughout. The urine was normal, the red blood count was 4.05 M., white blood count 11.1 T., hemoglobin 13.1 gm. per cent and a differential count of polymorphonuclear leukocytes 81 per cent; lymphocytes 14 per cent, stab forms 3 per cent and eosinophils 2 per cent. A posteroanterior chest film on admission revealed small, irregular densities, 1 to 2 mm. in diameter, diffusely scattered throughout the lung fields. These miliary-like densities had indistinct, irregular margins and were of uniform radiopacity. There was a closer relation to bronchial markings than to vascular ones. (Fig. 1.) The patient was given aureomycin, intravenous dextrose and saline. His temperature fell to 99.4°F. and he remained afebrile. The hospital course was one of rapid deterioration. Cyanosis of the mucous membranes and nail beds was noted and progressively deepened. Respirations gradually became shallow, the blood pressure fell and the patient expired on January 25, 1954, approximately thirty hours after admission.

At autopsy the significant findings were limited to the chest. The tracheobronchial tree was noted to be injected throughout and contained tenacious, purulent material. The lungs were markedly edematous and nodular on palpation. The cut surface of the formalin-fixed tissue blocks obtained from the Medical Examiner revealed the character of these nodules. (Fig. 2.) Most were from 1 to 2 mm. in

* The existence of this case was called to the attention of Chemical Corps Medical Laboratories after the autopsy had been performed. Material for examination was obtained from the Chief Medical Examiner, State of Maryland, and additional slides were obtained from the Armed Forces Institute of Pathology. Clinical data and x-ray films were supplied by the Prince Georges General Hospital, Maryland.

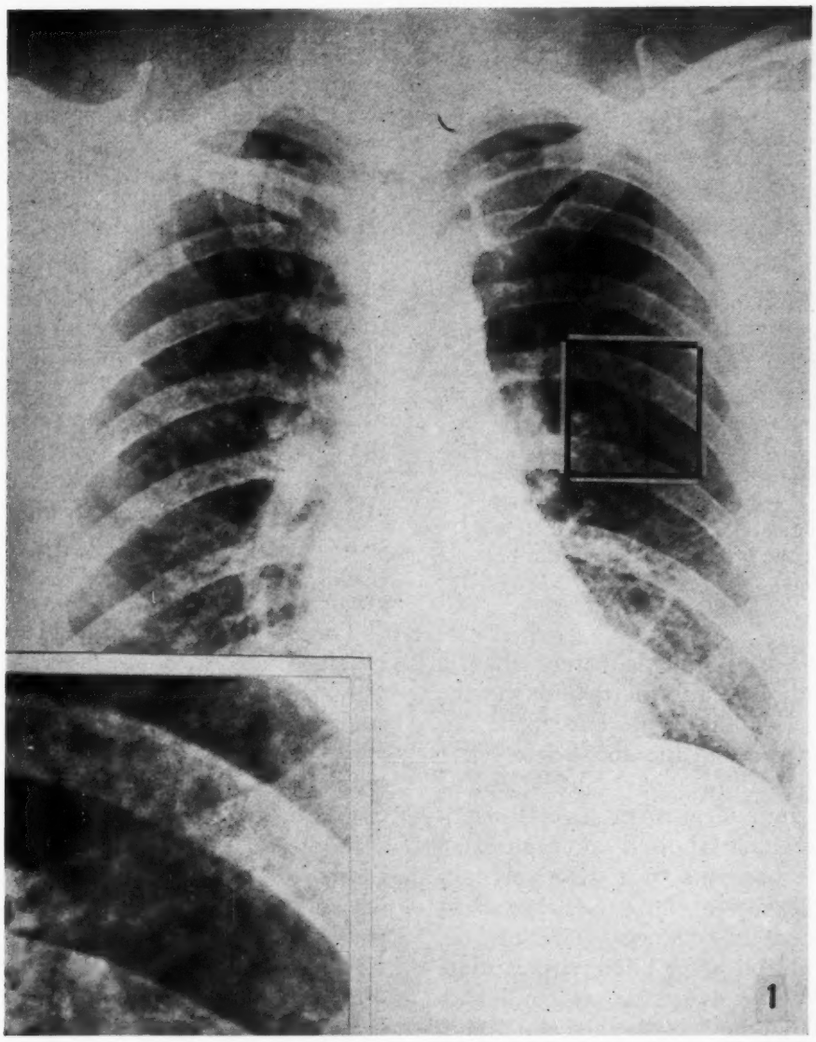

FIG. 1. Postero-anterior x-ray of the chest taken on January 24, 1954. Miliary-like densities may be seen diffusely scattered throughout both lung fields. The inset shows the details of the densities in their normal dimensions.

greatest dimension although occasional ones were somewhat larger. Their margins were so irregular as to be described as stellate. In the central portions of many were slit-like or round spaces representing bronchiolar lumens.

Histologically, all sections of the lung showed marked edema and many focal areas of hemorrhage. The characteristic lesion noted involved the bronchioles. (Fig. 3.) The lumen was virtually obliterated by organizing exudate which often projected in a polypoid fashion. Generally, a slit-like space separated the mass from a crescent of bronchiolar epithelium, in part showing hypertrophy of epithelial cells. Squamous metaplasia was not noted at this level of the bronchial tree. Within the organizing mass there was dense proteinaceous material and varying inflammatory cell infiltration. Although this proteinaceous material had a fibrinoid appearance, it was not characteristically stained with phosphotungstic acid-hematoxylin. Lymphocytes and monocytes were the predominant cells although polymorphonuclear leukocytes were also noted. Eosinophils were not conspicuous. The invading fibrous tissue was highly vascular, appearing as a delicate stroma with little collagen. The submucosa of the bronchiole was greatly swollen and infiltrated by inflammatory cells, lymphocytes being more prominent than polymorphonuclear leukocytes. There did not appear to be a significant degree of fibrosis of the submucosa. The muscular wall was essentially intact. The bronchial tree at this level is a multibranched structure with a muscularis

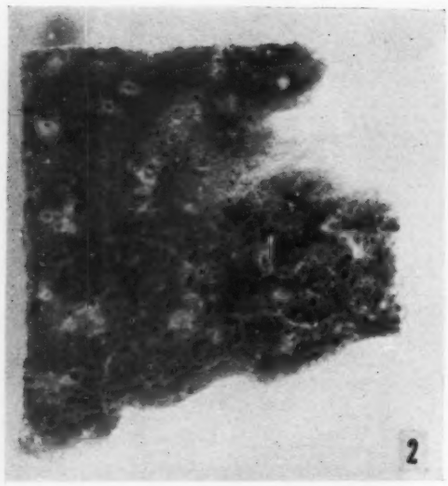

FIG. 2. The cut surface of a formalin-fixed block showing several of the nodules. Note that in many the bronchiolar lumen can be identified. × 2.

consisting of bands of muscle rather than a continuous sheath. Normal interruptions in the continuity of the wall therefore had to be differentiated from defects due to a destructive process. The bronchiole was cuffed almost exclusively by lymphocytes. The alveoli neighboring the bronchiole showed an organizing pneumonitis. In part this was relatively advanced with obliteration of the alveolar structures but more acute changes were also in evidence, some alveoli being filled with exudate composed chiefly of polymorphonuclear leukocytes. "Epithelialization" of the alveolar lining was commonly noted. There was no apparent alteration of the original lumen diameter of the bronchiole, as judged by the outline of the muscular wall. Bronchiolectatic lesions were conspicuous by their absence.

In none of the many sections examined were completely normal bronchiolar structures found. The minimally involved bronchiole (Fig. 4) possessed a completely intact and essentially normal mucosal epithelium. The submucosa, however, was moderately swollen and infiltrated by both lymphocytes and polymorphonuclear leukocytes. The muscularis was uninvolved but there was slight peribronchiolar scarring and infiltration by lymphocytes. Somewhat more advanced lesions were noted, still with the mucosa intact, in which the lumen was filled with exudate. Only when there were breaks in the continuity of the epithelial lining were masses of dense proteinaceous material present, and only in this circumstance did organization of the exudate occur. (Fig. 5.)

There appear to be two ways in which the exudate in the lumen of the bronchiole can become organized. On the one hand, this process appears to take place exclusively within the bronchiole. (Fig. 6.) Here one can readily make out the proliferating fibrous tissue arising in the granulating base of the submucosa. At least as often, however, this process of organization appears to be the result of invasion by the reactive process in the contiguous alveolar ducts and alveoli (Fig. 7), fibroblastic tissue arising from the organizing alveolitis invading the exudate within the bronchiole. Since alveoli arise from the respiratory bronchiole and alveolar duct as well as from the atrium and sacculus alveolaris, it is significant that the respiratory bronchiole seems to be the site of greatest organization.

The wall of the bronchiole remains essentially intact. (Fig. 8.) The elastica and muscularis showed no significant defects, the only interruptions being those due to the branching character of the structure. In the most advanced lesion the bronchiole was completely obliterated, as illustrated in Figure 9. In this instance, involving a respiratory bronchiole, the continuity of the organizing process within the lumen and of the process involving the surrounding alveolar structures is clearly evident. At the more peripheral locations in the lung it is often difficult to distinguish much more than a focal area of organization, as shown in Figure 10. There appear, however, to be some bands of smooth muscle even here. The focal nature of the lesion is probably significant. The entire tracheobronchial tree was evidently involved at some stage because foci of regenerated epithelium in the trachea still retain some characteristics of squamous epithelium, as illustrated in Figure 11.

COMMENTS

Careful consideration should be given to the use of the term bronchiolitis obliterans. Ehrich and McIntosh[18] maintained that the designation is justified only when the process is widespread. That similar lesions occur as focal phenomena in many organizing processes is well known; in fact, such organization may be widely disseminated. It is significant that these are often purely morphologic findings without clinical correlation and frequently not obliterating lesions at

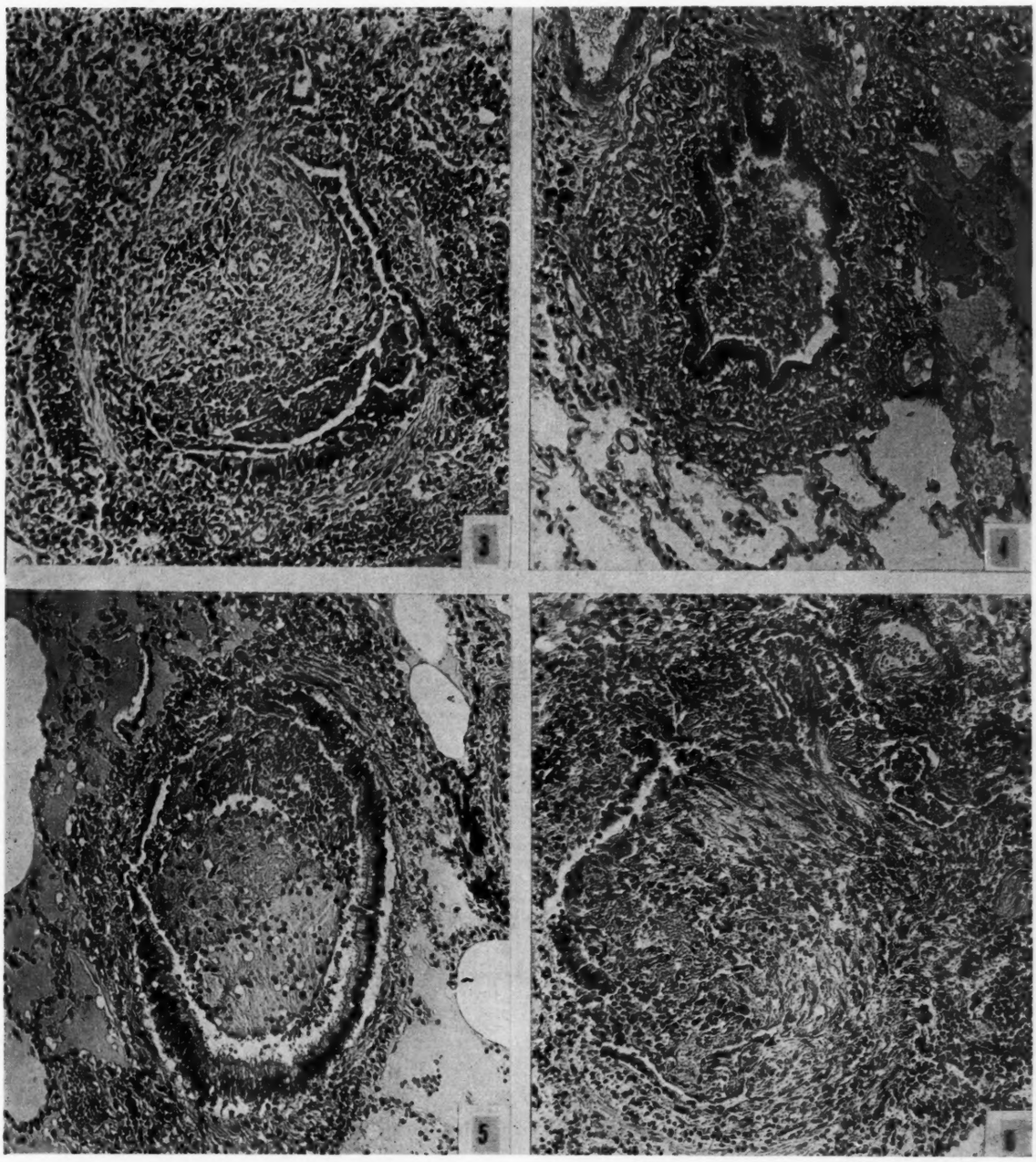

FIG. 3. The typical lesion of bronchiolitis obliterans showing the polypoid appearance of the occluding mass; hematoxylin and eosin stain.

FIG. 4. A minimally involved bronchiole. Possibly, a more distal section of this bronchiole would show involvement by the obliterating lesion; hematoxylin and eosin stain.

FIG. 5. Proteinaceous material in association with a defect of the bronchiolar mucosa; hematoxylin and eosin stain.

FIG. 6. Granulation tissue arising from the wall of the bronchiole and occluding the lumen; hematoxylin and eosin stain.

all but lesions of early fibroblastic proliferation. This objection might be raised with reference to Ehrich and McIntosh's three cases, all of uremic pneumonitis in which such phenomena as fibroblastic proliferation are extremely common. Considering the reserve ventilatory capacity of the lung, disseminated lesions would not be expected to produce the clinical picture seen with lesions of a generalized nature. Perhaps it would not be superfluous to speak of bronchio-

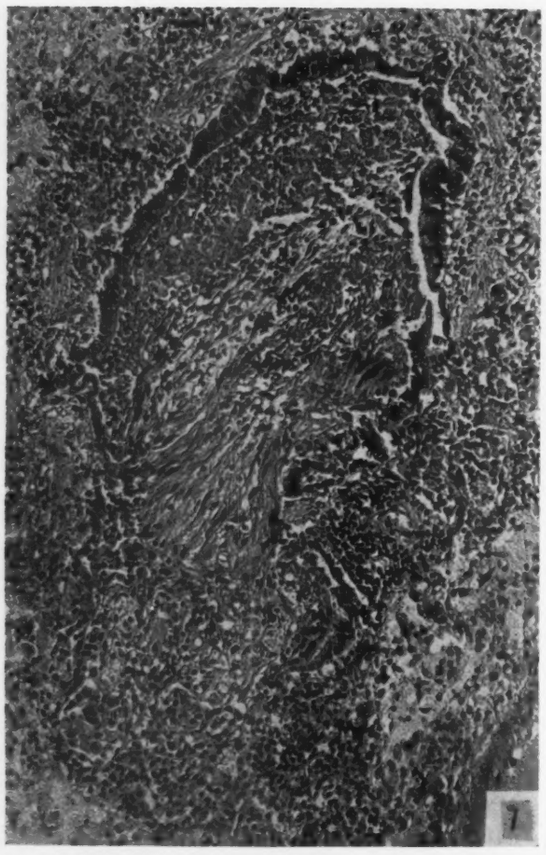

FIG. 7. Exudate in a bronchiole showing organization arising from the plastic process in contiguous alveoli; hematoxylin and eosin, × 115.

litis obliterans generalisata. The clinical picture is unique so that any purported case not accompanied by such features should be suspect.

There are additional facets of the case reported herein which are noteworthy. With respect to the question of the origin of the newly proliferated connective tissue, it is not surprising that a dual source was found: viz., from the granulating submucosa of the bronchiolar structure itself and as an ingrowth from alveolar structures. This is contrary to the belief of most authors, the general impression being that alveolar involvement is secondary. That alveoli may suffer primary damage is unquestionable where irritant fumes are concerned, and this is clearly demonstrated by Winternitz et al.[2] in their studies on war gas poisoning. Figure 12 is instructive in this respect, the section being that of lung from a dog exposed to red fuming nitric acid fumes at 75 ppm for five hours and dying five and a half hours from the time of onset of exposure. It shows unmistakable damage to the bronchiole and

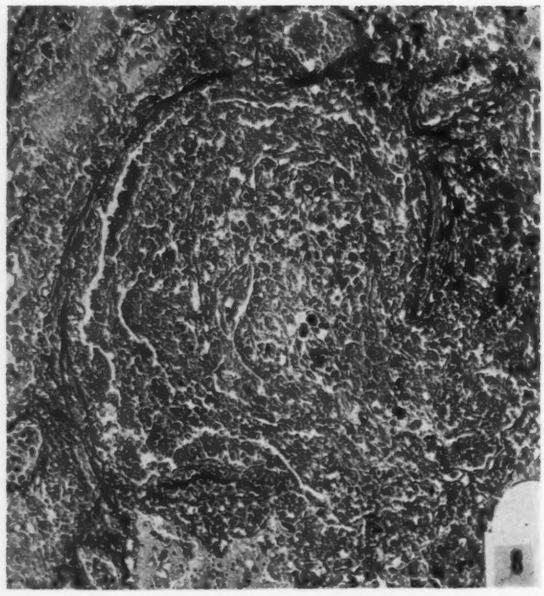

FIG. 8. A typical lesion of a bronchiole with normal elastica and muscularis; elastica, × 115.

alveolar duct, as well as necrosis of the alveolar septal wall. Such findings argue against the view that involvement of the bronchiole, short of the alveoli, is due to bronchoconstriction.[19] The dog is unique among mammals in respect to the degree to which the musculature of the respiratory bronchiole and alveolar duct is developed, and this might be correlated with isolated circumstances under which there are very marked increases in bronchial resistance. A more simple explanation of the level at which injury is maximum is based on the solubility of the material in question. Hydrochloric acid is more soluble in water than the oxides of nitrogen, and therefore the effects of hydrochloric acid are maximal in the upper airway, whereas those of the oxides of nitrogen are more deeply located.

There seems to be a segmental distribution of the lesions, for the total lesion is relatively uniform in size and considerably smaller in area than would correspond to a group of alveoli arising from a single bronchiole. Larger lesions seem to be predisposed to complete obliteration. The respiratory bronchioles and alveolar ducts appear to be the sites of maximal organization, and alveolar involvement predominantly affects alveoli arising direct from the respiratory bronchiole and alveolar duct.

From a nosologic standpoint, it is evident that bronchiolitis obliterans can be considered only when the full blown clinical as well as the

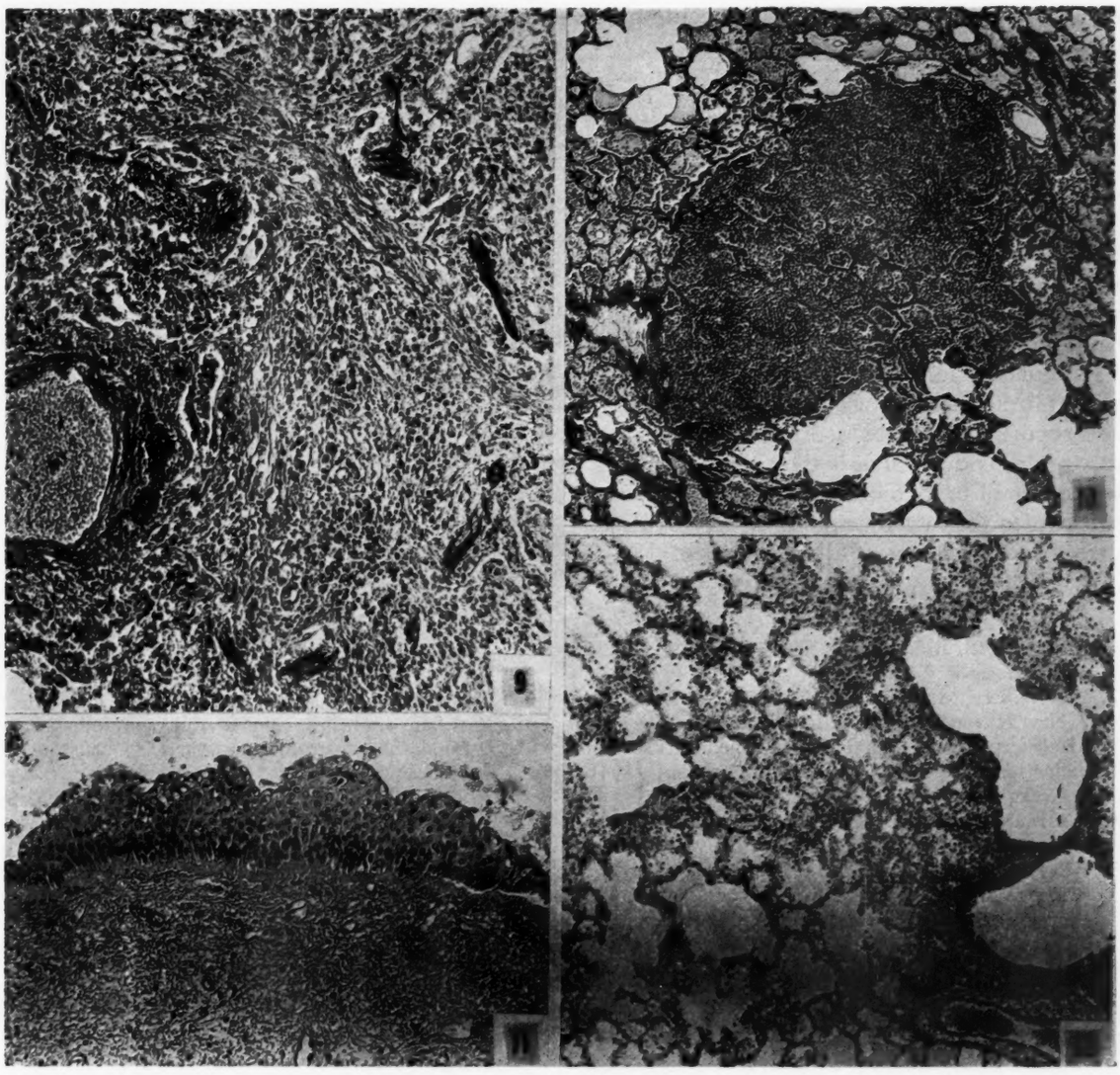

FIG. 9. Complete obliteration of a respiratory bronchiole showing continuity of the granulation tissue in the alveoli and bronchiolar lumen; elastica stain.

FIG. 10. A nodular area of organization in the periphery of the lung; elastica stain.

FIG. 11. An area of squamous metaplasia in the mucosa of the trachea; hematoxylin and eosin stain.

FIG. 12. Lung of dog exposed to red fuming nitric acid fumes. Note the necrotizing lesion of the respiratory bronchiole and alveolar duct as well as the focal alveolar necrosis; hematoxylin and eosin stain.

pathologic picture is present. The lucid description by Beitzke[15] of the manner in which bronchiolitis obliterans of infectious origin develops makes it clear that, apart from a greater inflammatory component, there is marked similarity with that due to chemical injury.

Poisoning by inhalation of irritant substances, in particular fumes of oxides of nitrogen, is by no means uncommon and in the past has accounted for the larger number of cases of bronchiolitis obliterans. Acute (pulmonary edema) rather than delayed fatalities are the rule, however.[3,9,10,23,26] Nitric acid, particularly red fuming and white fuming, is an extremely important substance in certain industries and today assumes added importance in its use as an oxidizer in rocket fuel. With the continued increase in the use of such substances, it is to be expected that there will be increasing numbers of similar industrial accidents. Physicians treating such patients should be alerted to this disease as a late complication. Furthermore, the increas-

ing effectiveness of treatment in the acute phase may mean that more patients will survive only to succumb at a later date.

SUMMARY

Bronchiolitis obliterans should be classified with the diseases of unremitting dyspnea. The clinical picture is distinctive and correlates with the generalized involvement of respiratory bronchioles by obstructing lesions. Of particular importance in diagnosis is a roentgen pattern simulating miliary tuberculosis.

Pulmonary infection or the inhalation of irritant fumes are the most common causes. The case reported herein was due to inhalation of nitrogen dioxide, which is the single most common cause of bronchiolitis obliterans. Attention is drawn to the fact that poisoning by oxides of nitrogen fumes is not at all uncommon.

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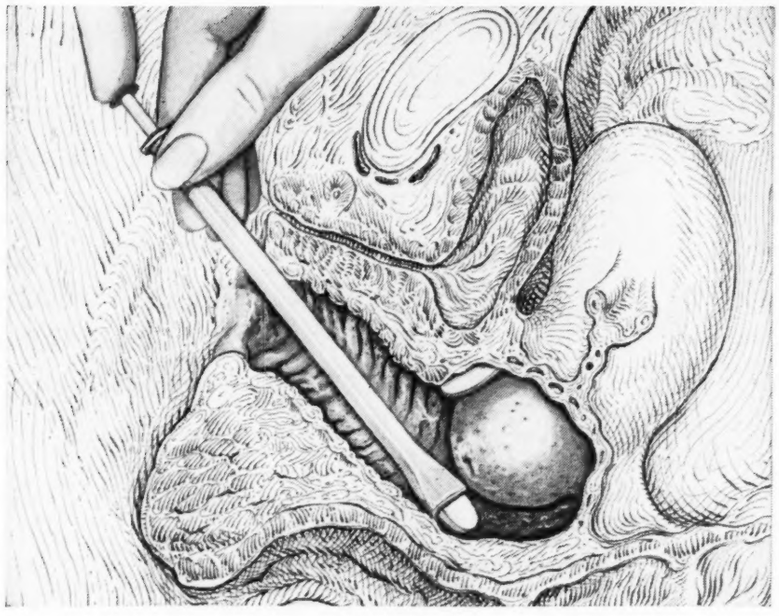

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DOSAGE:

One tablet after each meal and at bedtime. In children one year or older 0.6 cc. (10 drops); infants less than one year 0.3 cc. (5 drops): once daily diluted with water, milk, fruit or vegetable juice.

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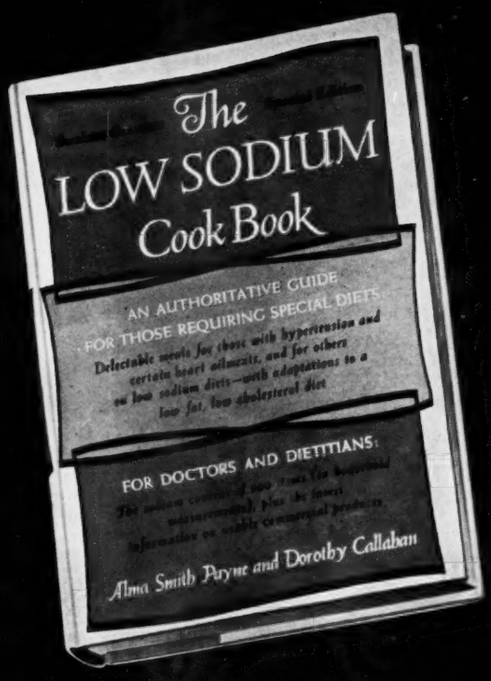

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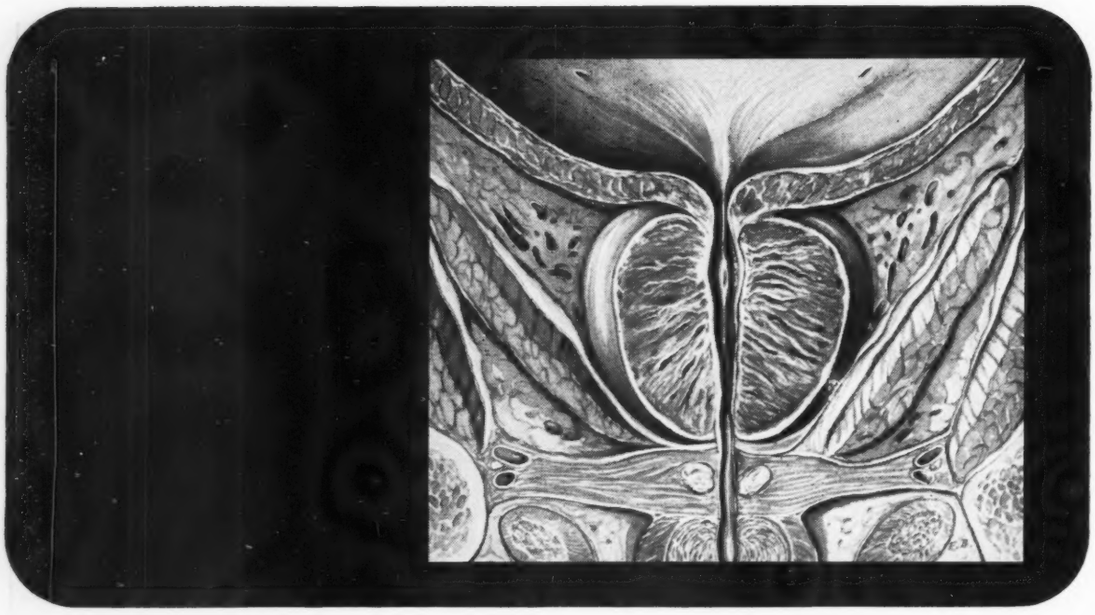

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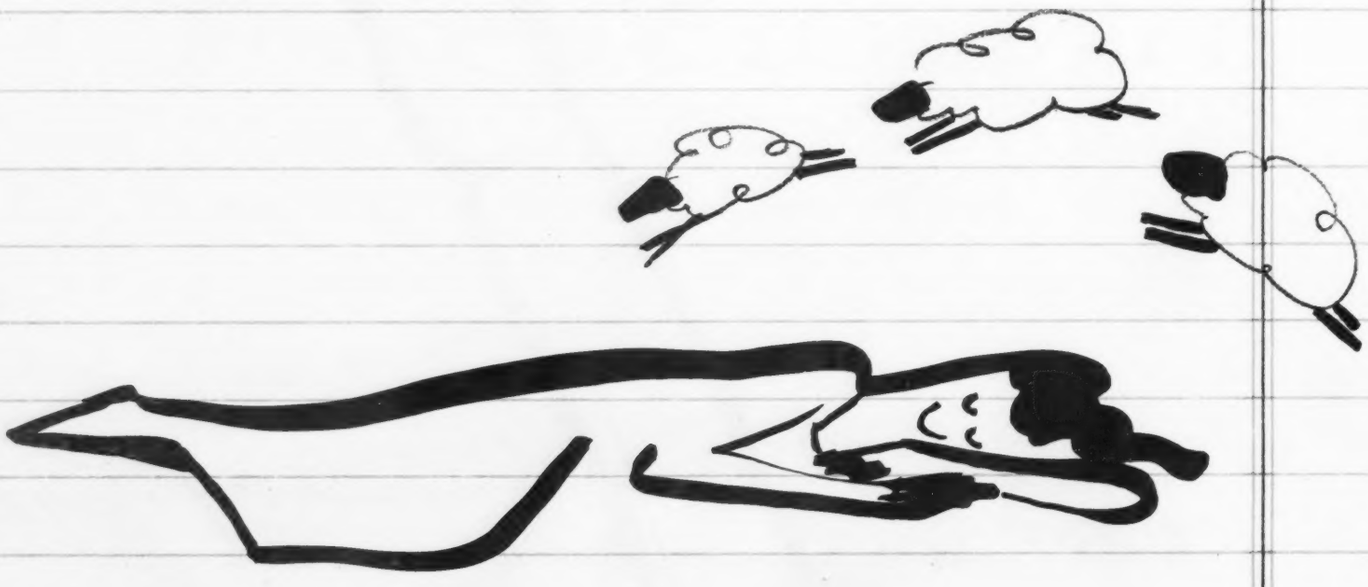

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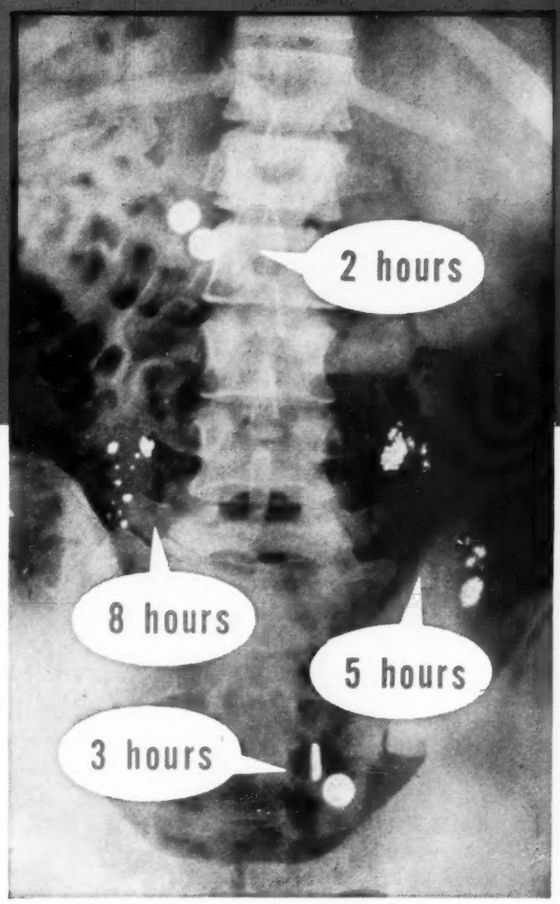

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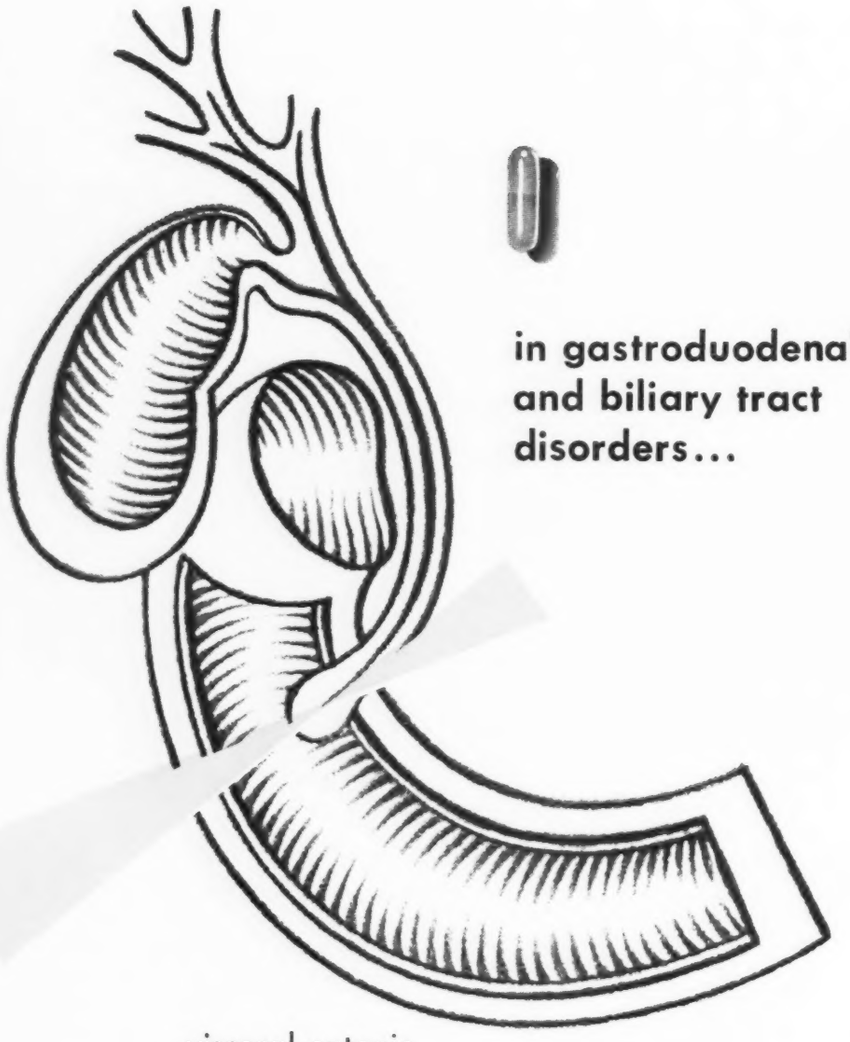

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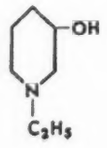

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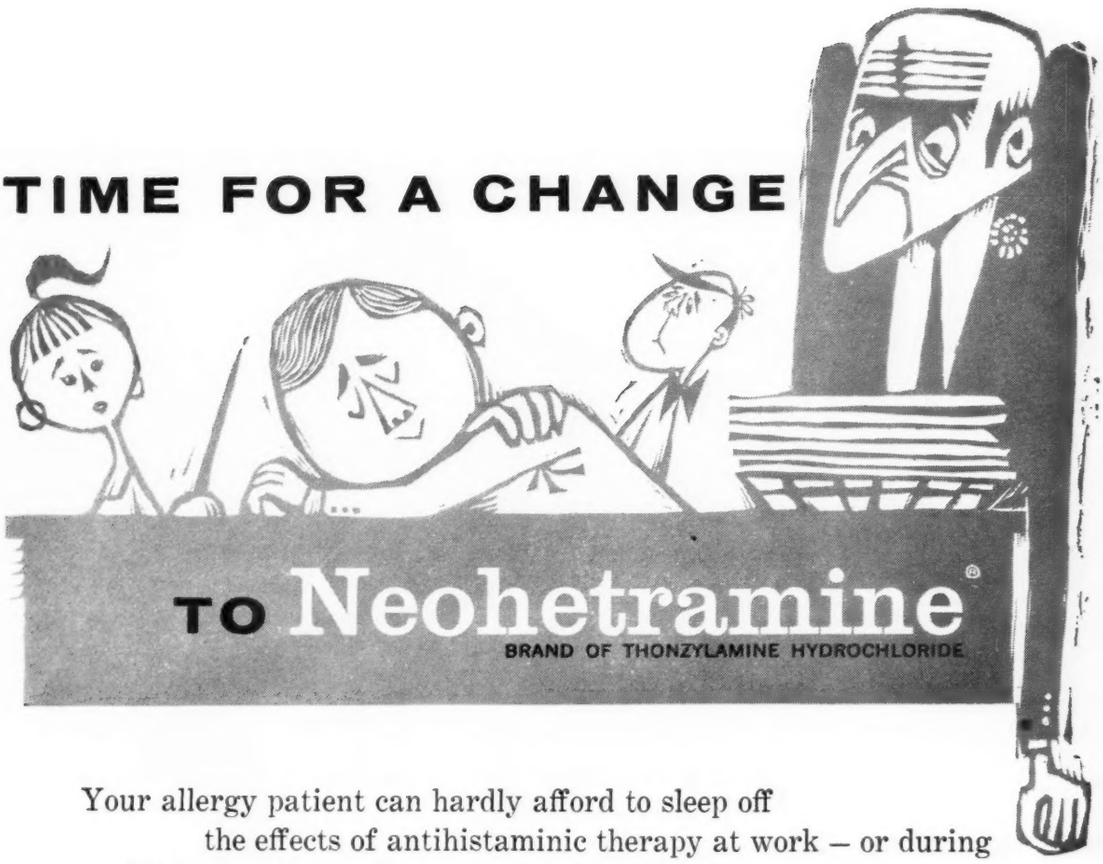

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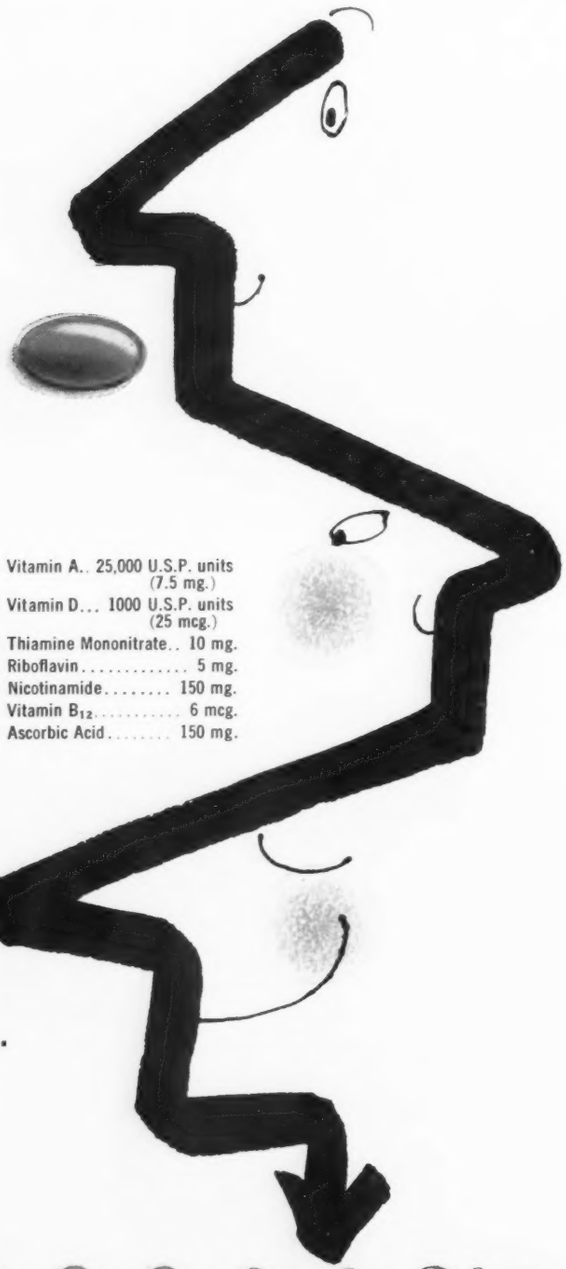

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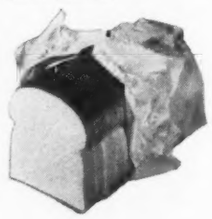
The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.



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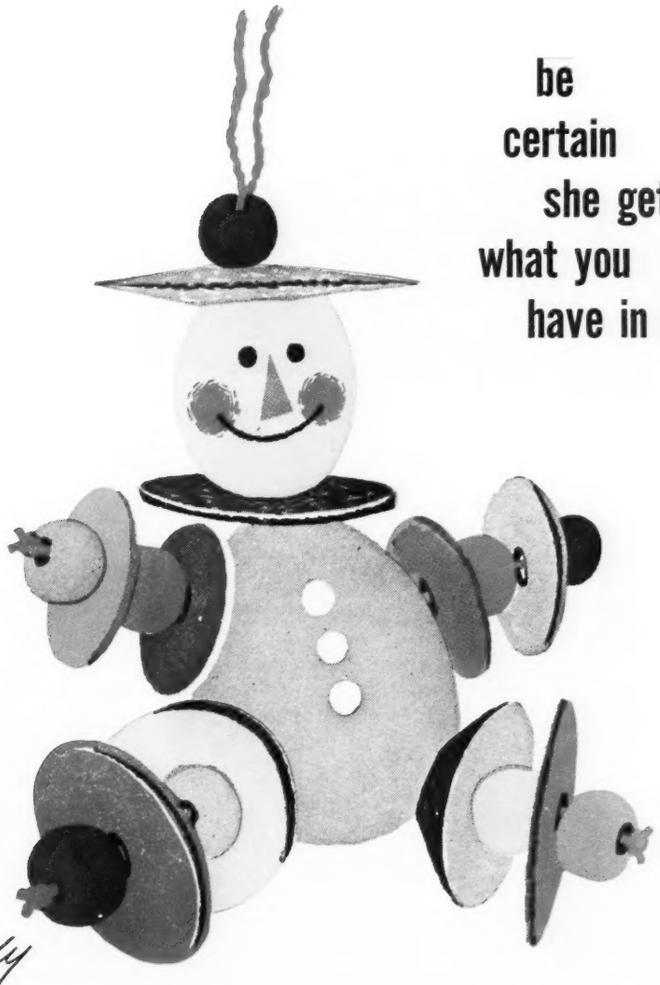

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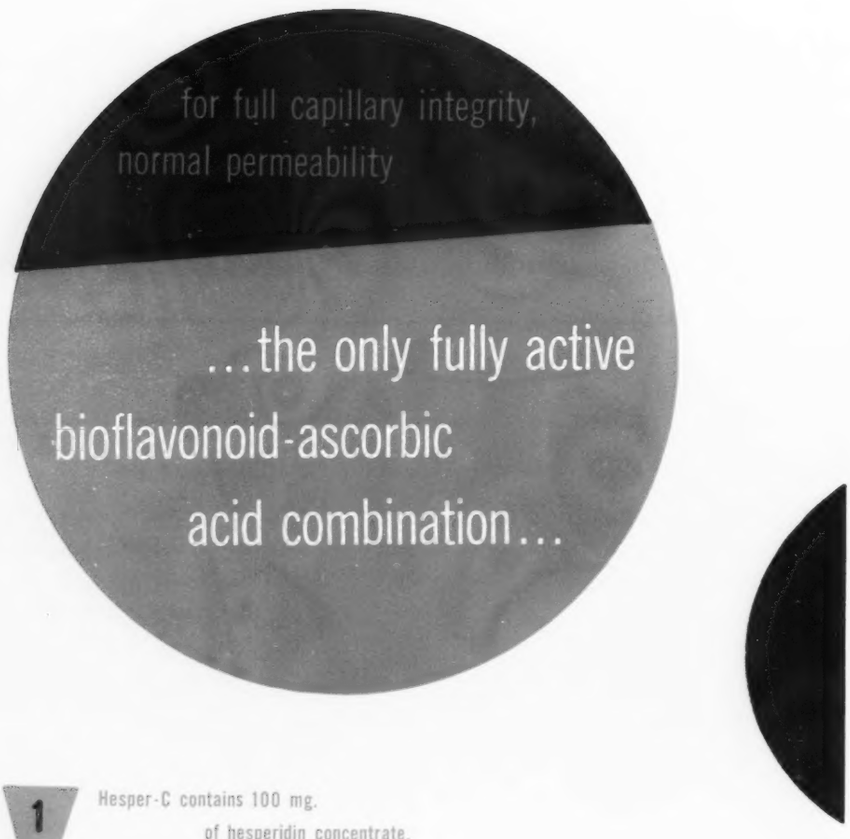

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---

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2. Cannon, P. R.; Frazier, L. E., and Hughes, R. H.: Factors Influencing Amino Acid Utilization in Tissue Protein Synthesis, in Symposium on Protein Metabolism, New York, The National Vitamin Foundation, Inc., 1954, pp. 55-90.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

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Finnerty, F.A., Jr.: Am. J. Med. *17*:629 (Nov.) 1954.

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" . . . [Rauwiloid] produces certain desirable effects such as mild sedation without somnolence and a general sense of well-being . . . "

Livesay, W.R., et al.: J.A.M.A. *155*:1027 (July 17) 1954.

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" . . . more than 70% of the patients said, unasked, that they felt better . . . 'I sleep better,' 'I am less jittery' and 'I feel good' were often heard."

Lipsett, M.B., et al.: California Med. *81*:412 (Dec.) 1954.

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Wilkins, R.W.: Mississippi Doctor *30*:359 (Apr.) 1953.

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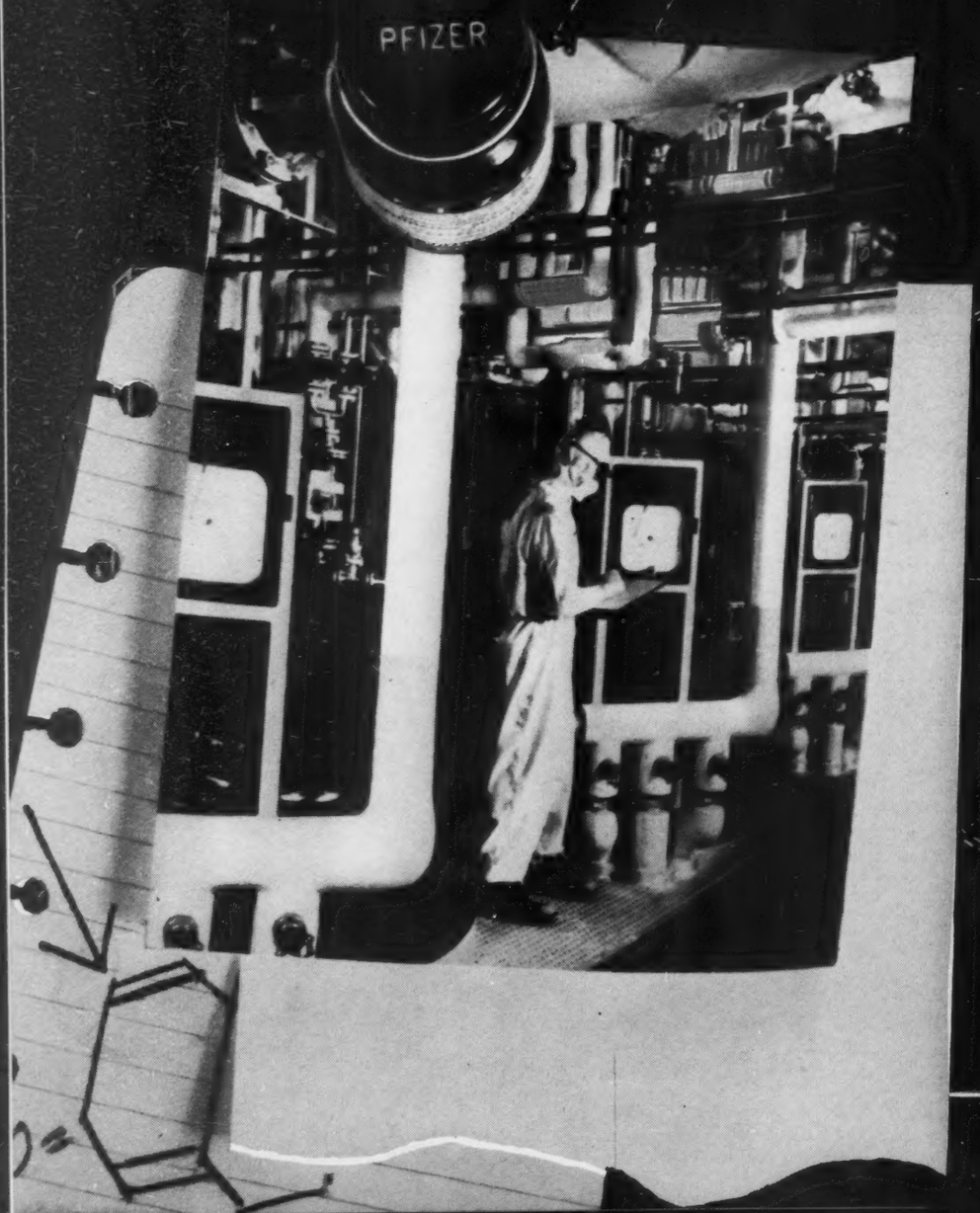

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3 to 5 times more potent than cortisone or hydrocortisone

***notable absence of major side effects*[1-3, 6]**

virtually without edema caused by sodium and water retention—avoids excessive potassium loss—other side reactions usually minor and frequently transient

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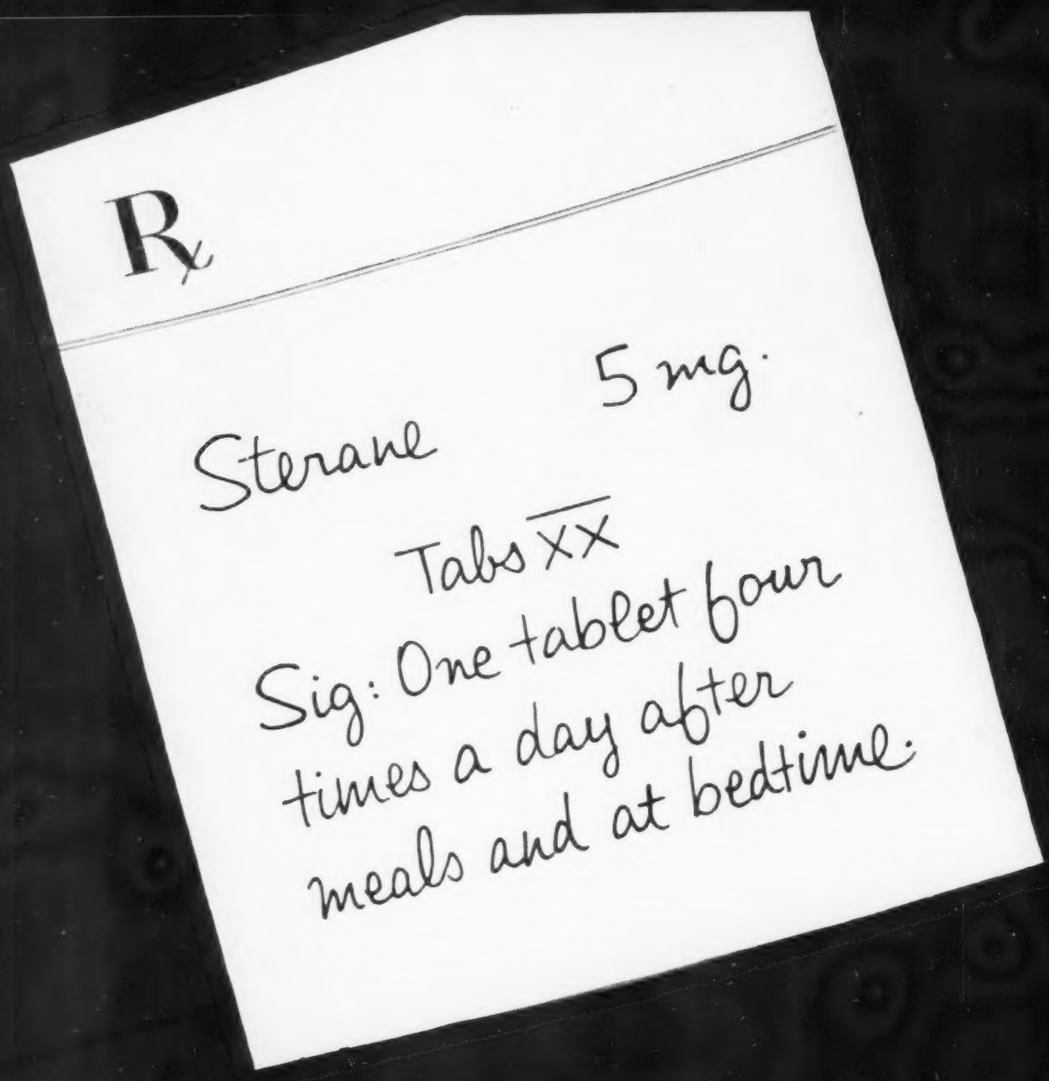

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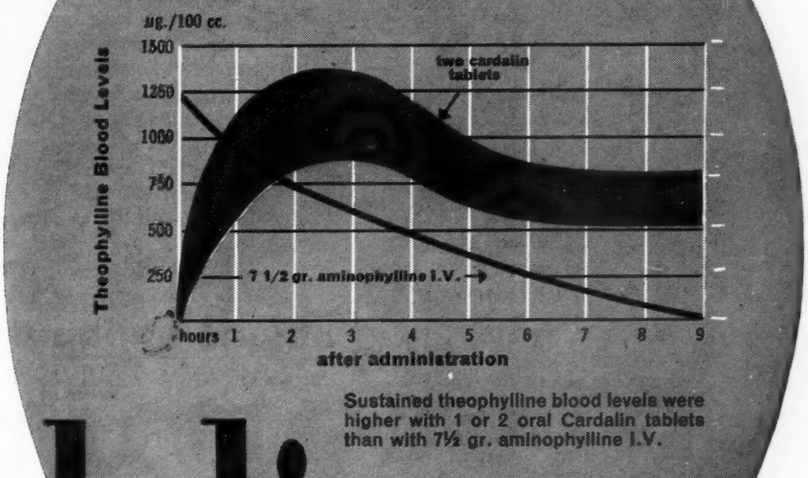

Sustained theophylline blood levels were higher with 1 or 2 oral Cardalin tablets than with 7½ gr. aminophylline I.V.

(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11: 301, 1953; and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100: 309, 1950.)

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References on the therapeutic efficacy of Cardalin

1. Segal, M. S., et al.: Quart. Rev. Allergy & Applied Immunol. 6: 399, 1952.
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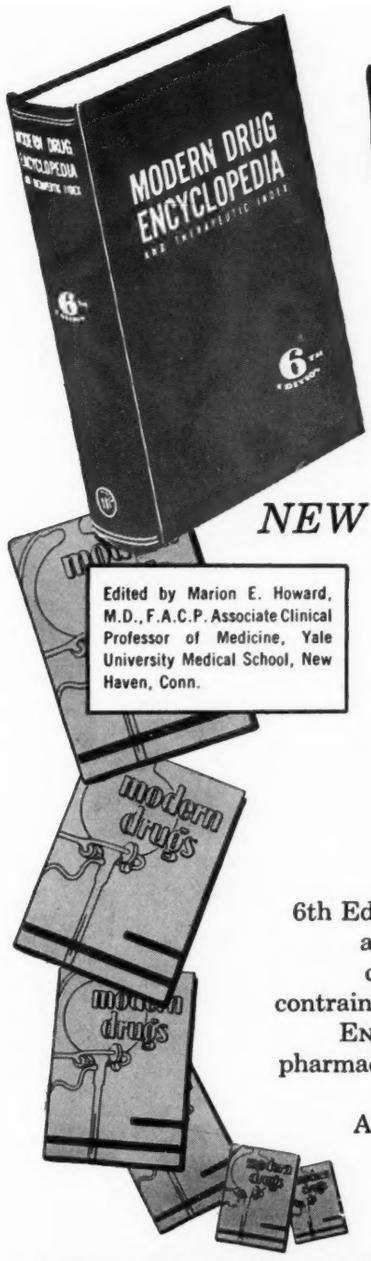

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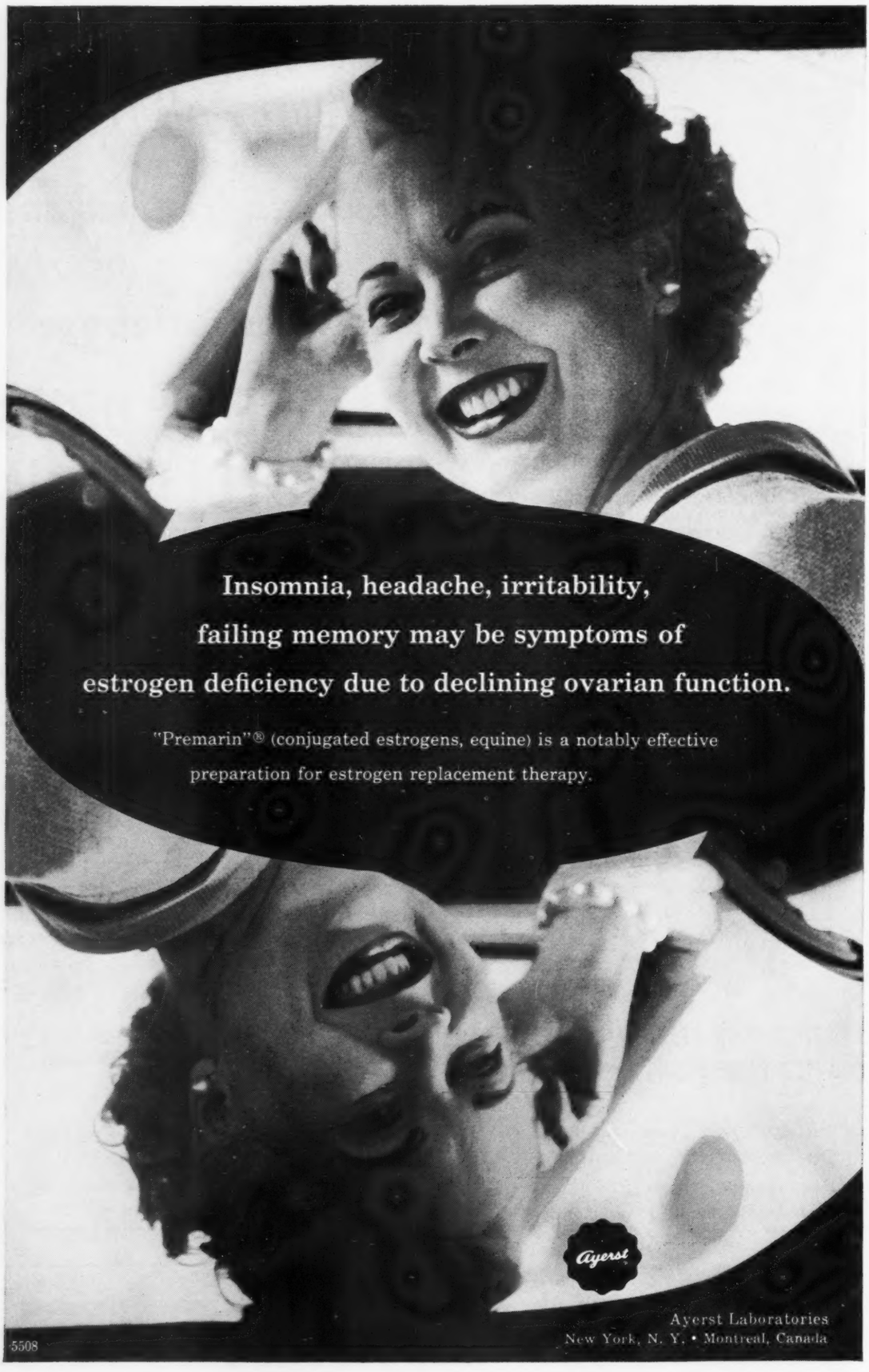
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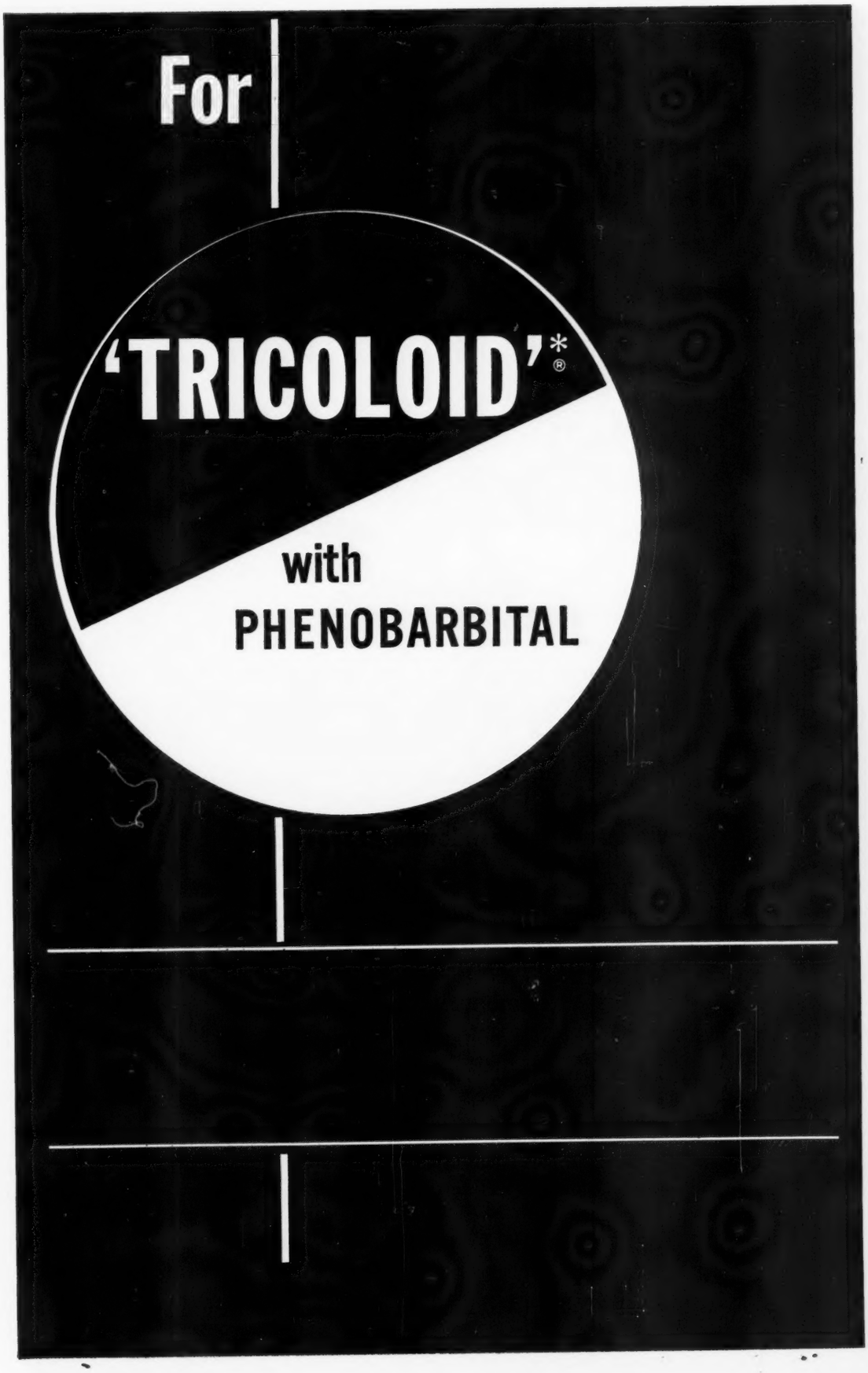
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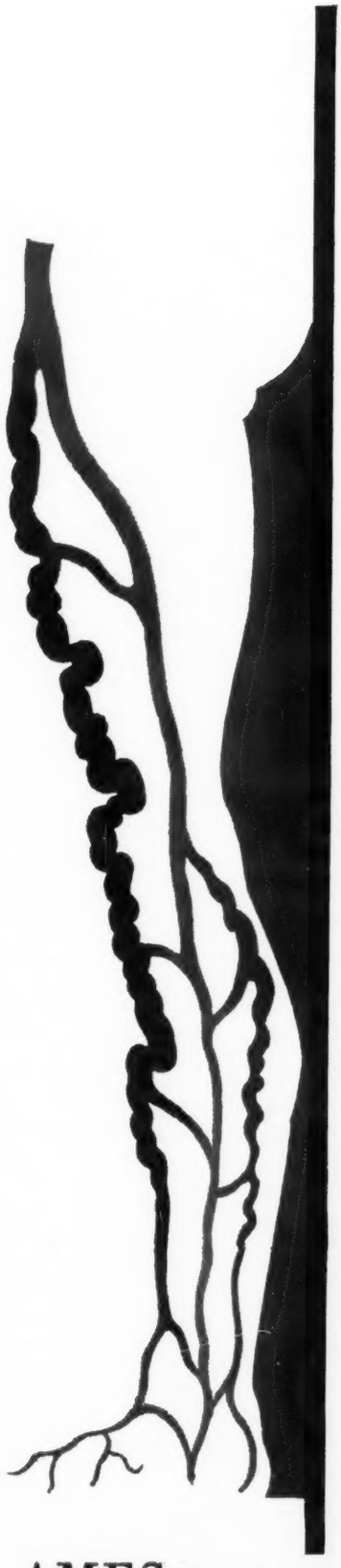

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